Surgical Treatments for Epilepsies in Children Aged 1–36 Months
A Systematic Review

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Abstract

Background and Objectives
Early life epilepsies (epilepsies in children 1–36 months old) are common and may be refractory to antiseizure medications. We summarize findings of a systematic review commissioned by the American Epilepsy Society to assess evidence and identify evidence gaps for surgical treatments for epilepsy in children aged 1–36 months without infantile spasms.

Methods
EMBASE, MEDLINE, PubMed, and the Cochrane Library were searched for studies published from 1/1/1999 to 8/19/21. We included studies reporting data on children aged 1 month to ≤36 months undergoing surgical interventions or neurostimulation for epilepsy and enrolling ≥10 patients per procedure. We excluded studies of infants with infantile spasms or status epilepticus. For effectiveness outcomes (seizure freedom, seizure frequency), studies were required to report follow-up at ≥12 weeks. For harm outcomes, no minimum follow-up was required. Outcomes for all epilepsy types, regardless of etiology, were reported together.

Results
Eighteen studies (in 19 articles) met the inclusion criteria. Sixteen prestudies/poststudies reported on efficacy, and 12 studies addressed harms. Surgeries were performed from 1979 to 2020. Seizure freedom for infants undergoing hemispherectomy/hemispherotomy ranged from 7% to 76% at 1 year after surgery. For nonhemispheric surgeries, seizure freedom ranged from 40% to 70%. For efficacy, we concluded low strength of evidence (SOE) suggests some infants achieve seizure freedom after epilepsy surgery. Over half of infants undergoing hemispherectomy/hemispherotomy achieved a favorable outcome (Engel I or II, International League Against Epilepsy I to IV, or >50% seizure reduction) at follow-up of >1 year, although studies had key limitations. Surgical mortality was rare for functional hemispherectomy/hemispherotomy and nonhemispheric resections. Low SOE suggests postoperative hydrocephalus is uncommon for infants undergoing nonhemispheric procedures for epilepsy.

Discussion
Although existing evidence remains sparse and low quality, some infants achieve seizure freedom after surgery and ≥50% achieve favorable outcomes. Future prospective studies in this age group are needed. In addition to seizure outcomes, studies should evaluate other important outcomes (developmental outcomes, quality of life [QOL], sleep, functional performance, and caregiver QOL).

Trial Registration Information
This systematic review was registered in PROSPERO (CRD42021220352) on March 5, 2021.
Onset of epilepsy in early life (age younger than 3 years) often has lifelong consequences. Seizures and disordered neuronal activity accompanying epilepsy can disrupt critical periods of development,1 and one-third of children diagnosed with epilepsy between 1 and 36 months will have drug-resistant epilepsy (DRE).2 Despite the importance of effective treatment, widespread treatment variability exists because epilepsy is not a single disorder but a heterogeneous group of disorders with numerous etiologies and varied natural histories.3

Most patients are initially treated with antiseizure medications (ASMs); however, after a first or second ASM fails to control seizures, the likelihood of sustained seizure freedom with any ASM substantially declines.4 In such contexts, other treatments including dietary therapy, surgery, or electrical stimulation devices are considered. Compared with other treatments, surgical treatments are distinctive in aiming to address underlying structural causes of epilepsies but are likely underused.5,6 Resection or disconnection of epileptogenic brain tissue can lead to seizure freedom (curative surgery) or seizure reduction (palliative surgery). Several factors may affect the outcomes including underlying pathology, surgery type, location, extent of resection, and concordance of presurgical evaluations. These factors affect judgements regarding epileptogenic zone identification and decisions regarding resection boundaries that aim to optimize benefits for seizure management while minimizing potential functional deficits.

Epilepsy specialists widely agree surgical treatment can be highly effective compared with serial trials of ASM in selected populations.7,8 Understanding current evidence for surgical treatment in early life epilepsy is critical for developing evidence-based treatment guidelines and identifying key evidence gaps. To date, systematic reviews, including a 2020 update by the National Institute for Health Care Excellence, have evaluated broader populations without focusing specifically on patients younger than 3 years of age.9

To assess existing evidence and characterize evidence gaps, the American Epilepsy Society (AES) identified the need for a systematic review of interventions for early life epilepsy. On behalf of the Agency of Healthcare and Quality (AHRQ) and the Patient-Centered Outcomes Research Institute (PCORI), we performed a systematic review assessing the treatment of epilepsy in children aged 1–36 months.10 In this publication, we summarize evidence on benefits and harms of surgical interventions.

Glossary

AES = American Epilepsy Society; AHRQ = Agency of Healthcare and Quality; ASM = anti-seizure medication; DRE = drug resistant epilepsy; HME = hemimegalencephaly; ILAE = International League Against Epilepsy; MCD = malformation of cortical development; QOL = quality of life; SOE = strength of evidence; VPS = ventriculoperitoneal shunt.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This systematic review was conducted in accordance with the AHRQ Methods Guide.11 The review protocol was posted on the AHRQ website for public comment and registered in PROSPERO (CRD42021220352).

Search Strategy

To inform scope and methods, we interviewed and incorporated feedback from 9 stakeholders including neurologists, neurosurgeons, dietitians, and nurse practitioners. A professional information specialist searched EMBASE, MEDLINE, PubMed, and the Cochrane Library for studies published from January 1, 1999, to August 19, 2021 (full search strategy in the eMethods supplemental data, links.lww.com/WNL/C432).

Inclusion Criteria

Studies were required to describe outcomes among children with epilepsy undergoing surgery from 1 to 36 months of age. We excluded studies assessing treatments for infantile spasms, metabolic epilepsies, status epilepticus, and acute symptomatic seizures. Infantile spasms were excluded because of differing biology, a comparatively well-defined evidence base, and unique treatment considerations. Studies were not required to include EEG confirmation of seizures. If studies reported a mix of patient ages/seizure types, we required the study to either (1) include ≥80% relevant population or (2) report relevant data separately as a subgroup.

All study designs were considered for inclusion. Studies were required to report data for ≥10 infants per procedure. Key outcomes included seizure freedom, seizure frequency, adverse effects, all-cause mortality, sudden unexplained death in an epilepsy patient, patient quality of life (QOL), and caregiver QOL. We also extracted other outcomes including neurodevelopment and sleep quality (see Supplemental data for full list of outcomes extracted). For effectiveness outcomes, studies were required to report outcomes at ≥12 weeks. For harms outcomes, there was no minimum follow-up. Seizure freedom was defined as International League Against Epilepsy (ILAE) 1,12 Engel Ia,13 or studies reporting “seizure freedom” with no further description. We also performed a sensitivity analysis to describe outcomes if seizure freedom included Engel I. For seizure frequency, favorable outcome was defined as >50% reduction in seizure frequency, Engel I or II, or ILAE I to IV.

Two analysts independently screened each abstract in DistillerSR, with disagreements resolved by consensus.
predetermined key outcomes, we rated the risk of bias using the ROBINS-I instrument for nonrandomized studies with control groups, and Evidence-based Practice Center guidance for studies without control groups. For key outcomes, we also rated strength of evidence (SOE) using the 2013 AHRQ Methods Guide recommendations, which uses domains including study design, risk of bias, consistency of results across trials, directness, and precision.

Data Availability
Study data will be made available on reasonable request for academic purposes.

Results
Searches identified 11,123 potential citations. After title and abstract screening, 41 studies met the inclusion criteria, of which 18 studies (in 19 articles) addressed surgical interventions. No studies addressed neuromodulation. Sixteen studies described efficacy and 12 reported harms.

Effectiveness of Surgical Interventions
Sixteen prestudies/poststudies (in 17 articles) described effectiveness of surgical interventions. Although we only included studies published after 1999, surgical procedures described in these studies were performed over nearly 4 decades (Figure 1). All studies were retrospective prechart/postchart reviews except for one which used registry data. The number of infants meeting the inclusion criteria from each study ranged from 10 to 58. Surgical interventions were broadly categorized as hemispherectomy/hemispherotomy (anatomical hemispherectomy, functional hemispherectomy, hemispherotomy) or nonhemispheric resections (e.g., multilobar, lobar, focal resections, or disconnections). Twelve studies described infants undergoing hemispherectomy/hemispherotomy, 8 described nonhemispheric resections, and 1 study focused only on tumor resections in infants with epilepsy due to malignancy.

Five studies were conducted in the United States. The remaining 11 non-US studies were conducted in Germany (n = 3), Japan (n = 2), Canada (n = 2), Italy (n = 2), Sweden (n = 1), or included data from multiple countries (n = 1). All US studies were single-center studies from the University of California at Los Angeles, University of Colorado, Cleveland Clinic, Boston Children’s Hospital, and Miami Children’s hospital. One study included data from 19 multinational centers with surgical procedures performed from 1999 to 2020. Data from 6 patients cared for at 2 of 19 centers (University of California at Los Angeles and Cleveland Clinic) may also have been included in other studies, given the overlap in periods (author correspondence).

For many studies, data represent either subgroups or individual patient data; thus, patient characteristics such as age, seizure etiology, and the length of follow-up were variably reported. No studies reported on race.
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Surgical procedure</th>
<th>Inclusion criteria</th>
<th>Seizure etiology or pathology</th>
<th>Seizure freedom</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemispherectomy/Hemispherotomy</strong></td>
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<tr>
<td>Cook et al. 200429</td>
<td>Anatomic hemispherectomy (n = 14) Functional hemispherectomy (n = 15) Hemispherotomy (n = 26)</td>
<td>Children with intractable seizures undergoing hemispherectomy at UCLA between 1986 and 2002</td>
<td>Cortical dysplasia</td>
<td>Combined: 42 of 55 (76%) Anatomical hemispherectomy: 12 of 14 (86%) Functional hemispherectomy/ hemispherotomy: 30 of 41 (73%)</td>
<td>2 years</td>
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<td>Jonas et al. 200430</td>
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<td>Lettori et al. 200726</td>
<td>Anatomic hemispherectomy (n = 6) Functional hemispherectomy or hemidecortication (n = 4)</td>
<td>Children with drug resistant epilepsy after ≥3 drugs at maximal dosage treated with hemispherectomy within 5 years of age at Catholic University (Italy)</td>
<td>7 HME, 2 dysplastic, 1 SWS</td>
<td>5 of 10 (50%)</td>
<td>1 year</td>
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<tr>
<td>Lodenkemper et al. 200722</td>
<td>Hemispherectomy (n = 14)</td>
<td>50 infants younger than 3 years old among 251 consecutive pediatric patients undergoing epilepsy surgery at Cleveland Clinic between 1989 and 2001</td>
<td>7 HME, 5 MCD, 2 SWS</td>
<td>9 of 14 (64%)</td>
<td>Median 6 months (range 4–42)</td>
</tr>
<tr>
<td>Otsuki et al. 201323</td>
<td>Hemispherotomy (n = 18)</td>
<td>Consecutive patients with cortical dysplasia and medically refractory epilepsy undergoing epilepsy surgery at aged younger than 6 at the National Center of Neurology and Psychiatry (Japan) from December 2000 to August 2011. Excluded patients with tuberous sclerosis, dysplastic tumors, and encephalomalacia</td>
<td>Cortical dysplasia</td>
<td>12 of 18 (66%)</td>
<td>NR</td>
</tr>
<tr>
<td>Pinto et al. 201433</td>
<td>Anatomic hemispherectomy (n = 10) Functional hemispherectomy (n = 4) Perinsular hemispherectomy (n = 1)</td>
<td>Children undergoing epilepsy surgery at Children's Hospital Boston from 1997 to 2011</td>
<td>Anatomic hemispherectomy patients: 6 HME, 1 polymicrogyria, 2 cortical dysplasia, 1 stroke Functional hemispherectomy/ perinsular hemispherotomy: 2 HME, 2 cortical dysplasia, 1 stroke</td>
<td>1 of 15 (7%)</td>
<td>≥1 year</td>
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<td>Reinholdson et al.  201518</td>
<td>Hemispherotomy (n = 12)</td>
<td>Swedish National Epilepsy Surgery Register data of children age younger than 4 years undergoing epilepsy surgery in Sweden between 1995 and 2010</td>
<td>7 HME, 2 polymicrogyria, 1 FCD I, 1 FCD unspecified, 1 gliosis/nonspecific</td>
<td>7 of 12 (58%)</td>
<td>2 years</td>
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<td>Roth et al. 202128</td>
<td>Hemispheric Procedures (n = 48)</td>
<td>All children undergoing epilepsy surgery at &lt;3 months or 100 days beyond 40 weeks gestation. For inclusion, infants were required to have ≥6 months of follow-up, unless the patient died</td>
<td>NR for this subgroup</td>
<td>70% (extrapolated to be 30 of 43)</td>
<td>Median 51 months (IQR 27 to 126)</td>
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<tr>
<td>Schramm et al. 201220</td>
<td>Hemispherotomy (n = 21)</td>
<td>All patients younger than 18 undergoing hemispherotomy at the Bonn University Medical Center (Germany) operated on between 1990 and the end of 2009 with ≥1 year follow-up.</td>
<td>NR for this subgroup</td>
<td>16 of 21 (76%)</td>
<td>≥1 year</td>
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Continued
Table 1 Seizure Freedom After Surgery, Study Characteristics (continued)

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Surgical procedure</th>
<th>Inclusion criteria</th>
<th>Seizure etiology or pathology</th>
<th>Seizure freedom</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 malformation of cortical development without HME (MCD), 2 MCD + ganglioma, 1 TS</td>
<td>7 of 10 (70%)</td>
<td>Median 6 months (range 4–42)</td>
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<tr>
<td>Multilobar, Lobar, or Focal Resection</td>
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<tr>
<td>Loddenkemper et al.</td>
<td>Focal cortical resection (n = 10)</td>
<td>50 infants younger than 3 years old among 251 consecutive pediatric patients (younger than 18 years old) undergoing epilepsy surgery at Cleveland Clinic between 1989 and 2001 were considered for inclusion</td>
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<td>200732</td>
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<td>7 of 10 (70%)</td>
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<tr>
<td>Reinholdson et al.</td>
<td>Frontal lobe resection (n = 12) Temporal lobe resection (n = 12)</td>
<td>Swedish National Epilepsy Surgery Register data of children aged younger than 4 undergoing resective epilepsy surgery in Sweden between 1995 and 2010</td>
<td>Temporal lobe resection: 2 focal cortical dysplasia II, 3 FCD unspecified, 4 low grade tumor, 1 TS Frontal lobe resection: 2 FCD II, 5 FCD unspecified, 2 gliosis or nonspecific, 2 TS, 1 vascular malformation</td>
<td>Combined: 12 of 24 (50%) Temporal lobe resection: 8 of 12 (67%) Frontal lobe resection: 4 of 12 (33%)</td>
<td>2 years</td>
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<tr>
<td>201518</td>
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<td>Sugimoto et al.</td>
<td>Focal cortical resection (n = 10)</td>
<td>Children, aged 0–3 years, who had epilepsy surgery at The Hospital for Sick Children, Toronto (Canada) from 1991 to 1996</td>
<td>NR</td>
<td>4 of 10 (40%)</td>
<td>Mean 3.2 years (range 0.25–6.7 years)</td>
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<td>199924</td>
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<tr>
<td>Kalbhenn et al.</td>
<td>Posterior disconnection (n = 10)</td>
<td>Consecutive patients undergoing posterior disconnection surgery between 2005 and 2017 for refractory posterior quadrantic epilepsy at Evangelisches Klinikum Bethel (Germany)</td>
<td>6 FCD, 2 ganglioma + FCD, 1 polymicrogyria, 1 meningeal angiomatosis</td>
<td>5 of 10 (50%)</td>
<td>2 years</td>
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<td>201921</td>
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<tr>
<td>Roth et al. 2021</td>
<td>Focal resections (n = 16)</td>
<td>All children undergoing epilepsy surgery at &lt;3 months or 100 days beyond 40 weeks gestation. For inclusion, infants were required to have ≥6 months of follow-up, unless the patient died</td>
<td>NR for this subgroup</td>
<td>56% (extrapolated to be 9 of 16)</td>
<td>Median 24 months (5-55 IQR)</td>
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</table>

FCD: Focal cortical dysplasia; HME: Hemimegalencephaly; MCD: Malformation of cortical development; NR: Not reported; TS: Tuberous sclerosis; SWS: Sturge-Weber syndrome.

* N provided by author correspondence.

* Follow-up duration for hemispherectomy and focal cortical resections combined.
Hemispherectomy/Hemispherotomy

Seizure Freedom
Eight retrospective prestudies/poststudies (in 9 articles) included 188 infants18,20,23,28-30,32,33 and reported on seizure freedom from 6 months to mean 4.3 years after surgery (Table 1). One study23 did not report the follow-up interval for the subgroup of included patients. All studies were assessed as a high risk of bias for many reasons including lack of a control group.

Seizure freedom rates at 1 year ranged from 7% to 76% (Figure 2). Six studies described outcomes at ≥1 year. Two larger studies reported seizure freedom rates of 76% (42/55)29 and 70% (30/43)28 at 2 years and median 4.3 years, respectively. Three smaller studies reported rates ranging from 50% to 76%.18,20,26 Finally, 1 study reported only 7% (1/15) infants were seizure free at follow-up of ≥1 year after surgery.33

We used a stringent definition of seizure freedom, which required studies using the Engel classification to report Engel Ia. However, if we had considered Engel I as seizure freedom, seizure freedom in Pinto et al.33 would increase to 66% (10 of 15); also, 4 other studies19,22,25,31 reporting rates of 55%–81% (consistent with the range of seizure freedom rates we already identified) would have been included.

Notably, prestudies/poststudies lack true control groups, posing a challenge for knowing what would have happened had these patients not undergone surgery. However, most infants underwent surgery for intractable epilepsy, suggesting none would have experienced seizure freedom without surgery. In addition, although seizure counts were assessed using retrospective data from charts (i.e., not captured in the context of a trial), seizure freedom is less subject to recall bias or other types of bias than other outcomes such as seizure frequency. Thus, we concluded that low strength evidence suggests some infants with intractable epilepsy achieve seizure freedom after hemispherectomy/hemispherotomy (Table 2).

Seizure Frequency
Nine retrospective prestudies/poststudies (including 186 infants) reported on seizure frequency. All studies reported more than half of infants achieved a favorable outcome (Engel I or II, ILAE I to IV, or >50% seizure reduction). The proportion of infants achieving favorable outcome ranged from 67% to 100%, with most studies reporting a follow-up of at least 1 year. Specifically, studies reported the following proportion of infants had favorable outcomes at follow-up: 67% (10/15),33 72% (13/18),23 73% (35/48),25 72% (31/43),28 80% (8/10),22 88% (14/16),31 92% (11/12),18 93% (13/14),32 and 100% (10/10).26 However, seizure counts were assessed using retrospective data from charts (i.e., not captured in the context of a trial), which we assessed as high risk of bias. Thus, the evidence was considered insufficient to draw a conclusion regarding seizure frequency.

Favorable outcome after epilepsy surgery could depend on multiple factors, including underlying etiology. Eight studies21,22,24,26,31,32,34 reported individual patient data for pathology or etiology, surgical intervention, and outcomes including 65 infants undergoing hemispherectomy or hemispherotomy. Seizure etiology or pathology was reported as hemimegalencephaly (HME) (58%), focal cortical dysplasia (FCD) or malformation of cortical development (MCD) without HME (20%), or other pathology (22%). A summary analysis found the proportion of infants achieving favorable outcomes was similar across these 3 groups: 89% (34/38).
for HME, 92% (12/13) for FCD/MCD without HME, and 93% (13/14) for other pathology.

**Nonhemispheric Surgical Procedures**

**Seizure Freedom**

Five pre-studies/poststudies including 70 infants reported on seizure freedom. Infants underwent focal cortical resections in 3 studies,\(^{18,24,28,32}\) frontal or temporal lobe resection in 1 study,\(^{18}\) and posterior disconnection in 1 study.\(^{21}\) The rates of seizure freedom ranged from 40% to 70%. Figure 3 presents seizure freedom rates and follow-up durations. Specifically, focal resection was followed by seizure freedom in 70% (7/10),\(^{32}\) 56% (9/16),\(^{28}\) and 40% (4/10)\(^{34}\) at a median 6, 24 months, and mean 3.2 years, respectively. Kalbhenn et al.\(^{21}\) reported that 50% (5/10) of patients were seizure free after posterior disconnection surgery at 2 years after surgery. Reinholdson et al.\(^{18}\) reported 50% (12/24) of children undergoing frontal or temporal lobe resection were seizure free at 2 years after surgery. If seizure freedom had included studies reporting Engel I, 3 additional studies reporting the rates of 62%,\(^{19}\) 69%,\(^{34}\) and 91%\(^{25}\) would have also been included.

We concluded some infants with intractable epilepsy achieve seizure freedom after intralobar, multilobar, or focal cortical resection (SOE: Low).

**Seizure Frequency**

Seven retrospective pre-studies/poststudies including 148 infants reported seizure frequency. Six of 7 studies reported seizure frequency data that allowed for determination of favorable outcome for seizure frequency.\(^{18,24,25,28,32,34}\) All studies found more than half of infants achieved a favorable outcome for seizure frequency: specifically, the proportion of infants achieving favorable outcomes was 50% (5/10),\(^{24}\) 83% (20/24),\(^{18}\) 85% (11/13),\(^{34}\) 90% (52/58),\(^{25}\) 94% (15/16),\(^{28}\) and 100% (10/10).\(^{32}\) The mean follow-up was ≥1 year after surgery for all studies. A seventh study\(^{19}\) reported of 17 infants for whom the extent of final resection was intralobar, 76% (13/17) were Engel I, whereas 24% (4/17) were Engel II

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*One study\(^{19}\) only reported a percentage and thus was not included in this number.*
to IV. Nevertheless, because of a high risk of bias, evidence was judged insufficient to draw a conclusion.

Studies reporting individual patient data included 43 infants undergoing multilobar, lobar, or focal resection. Seizure etiology or pathology was FCD/MCD without HME (56%) or other pathologies (44%). A simple summative analysis found the proportion of infants with favorable outcome rates was 67% (16/24) for FCD/MCD without HME and 74% (14/19) for other pathologies.

**Tumor Resection**

One retrospective chart review27 focused exclusively on 20 infants with epilepsy because of primary supratentorial brain tumors. Mean time from tumor diagnosis to surgery was 0.86 (SD 0.63) months. Of 17 patients with 8 years postoperative follow-up, 53% (9/17) were Engel I, 24% (4/17) Engel II, 12% (2/17) Engel III, and 12% (2/17) Engel IV.

**Developmental Outcomes (All Procedures)**

Only 4 prestudies/poststudies reported on developmental outcomes including developmental quotient [DQ], language, or functional status. Three studies26,30,32 focused on hemispherectomy, including 2 studies reporting DQ after hemispherectomy. Loddenkemper et al.32 included 24 infants undergoing hemispherectomy or focal resection at a median age of 14 months (3–34). Infants were evaluated at a median 12 months (3–34) preoperatively and at a median 24 months (10–53) after surgery. The proportion of infants with developmental delay (DQ < 70) decreased after surgery, but was not statistically significant (p = 0.125). Furthermore, 52% (26/50) of consecutive infants were excluded because of incomplete data or the use of other neuropsychological tests, potentially limiting generalizability. Jonas et al.30 found that in 16 infants undergoing hemispherectomy for HME, at 6–24 months after surgery, the Vineland DQ increased by 9.1 (SD 16) compared with presurgery. The spoken language rank also increased from 0.33 (SD 0.5) to 1.4 (SD 1.8) after surgery. Lettori26 included 10 infants meeting the inclusion criteria and undergoing hemispherectomy. Before surgery, 20% (2/10) had a dependent functional status, and functional status could not be assessed for 80% (8/10). After surgery, 6 were dependent, 3 semiindependent, and 1 independent.

Finally, one study reported some infants had improvement in developmental delay after undergoing focal cortical resection (8/10 with delay preoperatively, 6 infants with improved/good status after surgery).24 However, the study did not report how delay was assessed.

**Harms**

Twelve prestudies/poststudies described harms after surgery (Table 3).

**Hemispherectomy/Hemispherotomy**

Eleven prestudies/poststudies18,19,22,23,25,26,28,29,31,33,35 reported harms after hemispherectomy/hemispherotomy. Roth et al.28 included data from 19 centers with surgical procedures performed from 1999 to 2020. Seven patients cared for at 3 of 19 centers (University of California at Los Angeles, Cleveland Clinic, and Great Ormond Street Hospital) may also have been previously reported in other studies included in this report (author correspondence).29,32,35 Iwasaki et al.36 described harms for 75 infants, of which 9 hemispherectomy patients had previously been described in another study,23 also included in this report (author correspondence).

**Mortality**

Nine prestudies/poststudies reported on mortality after hemispherectomy/hemispherotomy. For the outcome of surgical mortality, studies were assessed as low risk of bias. Studies described mortality after anatomical hemispherectomy (3 studies), functional hemispherectomy or hemispherotomy (8 studies), or across multiple procedures (lesionectomy, cortical resection, and hemispherectomy/hemispherotomy, 1 study).
<table>
<thead>
<tr>
<th>Author</th>
<th>(Year)</th>
<th>Surgical procedure (n)</th>
<th>Inclusion criteria</th>
<th>Seizure etiology or pathology</th>
<th>Harms reported (follow-up interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cook et al.</td>
<td>2004</td>
<td>Anatomical hemispherectomy (n = 14), Functional hemispherectomy (n = 15), Hemispherotomy (n = 26)</td>
<td>Children with intractable seizures undergoing hemispherectomy at UCLA between 1986 and 2002</td>
<td>Cortical dysplasia</td>
<td>Mortality (NR), Other AEs</td>
</tr>
<tr>
<td>Dunkley et al.</td>
<td>2010</td>
<td>Anatomical hemispherectomy (n = 2), Functional hemispherectomy (n = 25), Multilobar/Lobar/Focal Resection (n = 15)</td>
<td>All children undergoing resection for epilepsy at younger than 36 months of age and followed up for at least 2 years at Great Ormond Street Hospital</td>
<td>NR by procedure</td>
<td>Mortality (NR), VP or LP shunt placement (placed at 6 weeks, 6 months, 12 months, 4 years)</td>
</tr>
<tr>
<td>Iwasaki et al.</td>
<td>2015</td>
<td>Hemispherotomy (n = 10)</td>
<td>Consecutive patients undergoing hemispherotomy for treatment of intractable epilepsy in Tohoku University Graduate School of Medicine between 2001 and 2012</td>
<td>NR</td>
<td>Mortality (NR), VP shunt (NR)</td>
</tr>
<tr>
<td>Kadish et al.</td>
<td>2019</td>
<td>Hemispherotomy (n = 22)</td>
<td>Consecutive patients undergoing presurgical evaluation at Epilepsy Center Freiburg (Germany) with follow-up &gt; 1 year after surgery</td>
<td>NR by procedure</td>
<td>Mortality (&quot;Perioperative&quot;), VP shunt (NR), Other AEs</td>
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<tr>
<td>Kumar et al.</td>
<td>2015</td>
<td>Hemispherotomy (n = 16)</td>
<td>All children under the age of 1 year undergoing surgical intervention to treat medically refractory epilepsy at Children's Hospital of Colorado between 2002 and 2013</td>
<td>NR</td>
<td>Mortality (&quot;Perioperative&quot;), Hydrocephalus (mean follow-up for study 56 months, range 3–133 months), Other AEs</td>
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<tr>
<td>Lettori et al.</td>
<td>2007</td>
<td>Anatomic hemispherectomy (n = 6), Functional hemispherectomy or hemidecortication (n = 4)</td>
<td>Patients treated with hemispherectomy within 5 years of age in the Child Neurosurgery Unit of Catholic University, Rome from 1980 to December 2003, &quot;we enrolled in the study only 19 thoroughly studied children, drug resistant with at least 3 drugs at maximal dosage with no seizure control&quot;</td>
<td>7 HME, 2 dysplastic, 1 SWS</td>
<td>Hydrocephalus (NR), Other AEs</td>
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<tr>
<td>Otsuki et al.</td>
<td>2013</td>
<td>Hemispherotomy (n = 18)</td>
<td>Consecutive patients with cortical dysplasia and medically refractory epilepsy undergoing epilepsy surgery at age &lt;6 at the National Center of Neurology and Psychiatry (Japan) from December 2000 to August 2011. Excluded patients with tuberous sclerosis, dysplastic tumors, and encephalomalacia</td>
<td>Cortical dysplasia</td>
<td>Mortality (NR)</td>
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<td>Pinto et al.</td>
<td>2014</td>
<td>Anatomic hemispherectomy (n = 10), Functional hemispherectomy (n = 4), Peri-insular hemispherectomy (n = 1)</td>
<td>Children undergoing epilepsy surgery (anatomic hemispherectomy, functional hemispherectomy, and peri-insular hemispherectomy) at Children's Hospital Boston from 1997 to 2011. Excluded patients with progressive disease including Rasmussen encephalitis and Sturge-Weber syndrome</td>
<td>Anatomic hemispherectomy patients: 6 HME, 1 polymicrogyria, 2 cortical dysplasia, 1 stroke Functional hemispherectomy/Peri-insular hemispherectomy: 2 HME, 2 cortical dysplasia, 1 stroke</td>
<td>VP shunt (NR)</td>
</tr>
<tr>
<td>Reinholdson et al.</td>
<td>2018</td>
<td>Hemispherotomy, Frontal lobe resection, Temporal lobe resection</td>
<td>Swedish National Epilepsy Surgery Register data capturing population based, observational cohort of children under 4 years of age undergoing resective epilepsy surgery in Sweden between 1995 and 2010</td>
<td>7 HME, 2 polymicrogyria, 1 FCD I, 1 FCD unspecified, 1 gliosis/nonspecific</td>
<td>VP shunt (within 2 years after surgery)</td>
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<td>Author (Year)</td>
<td>Surgical procedure (n)</td>
<td>Inclusion criteria</td>
<td>Seizure etiology or pathology</td>
<td>Harms reported (follow-up interval)</td>
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<td><strong>Roth et al. 2021</strong>&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Hemispheric surgeries (25 peri-insular, 12 vertical functional hemispherectomies, 10 anatomical hemispherectomies, 1 unknown) Focal resections (7 lobectomies, 12 lesionectomy)</td>
<td>Epilepsy surgery at &lt;3 months age or 100 days beyond 40 weeks gestation at one of 19 centers. For inclusion, infants were required to have 26 months of follow-up, unless the patient died. Excluded infants with epilepsy because of hypoxic ischemic encephalopathy.</td>
<td>28 cortical dysplasia, 17 hemimegalencephaly, 5 tubers, 4 nonspecific findings, 1 glioneural hamartoma, 1 stroke, 1 Sturge Weber, 1 hematoma, 6 unknown</td>
<td>Mortality (“Perioperative”) Hydrocephalus (median follow-up for all study outcomes 51 months, IQR 21 to 126) Other AEs (combined incidence across all procedures)</td>
<td></td>
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<td><strong>Iwasaki et al. 2021</strong>&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Hemispherotomy (peri-insular hemispherotomy, vertical parasaggital hemispherotomy) (n = 27) Multilobar surgery, Unilobar surgery (n = 48)</td>
<td>Infants undergoing “first curative epilepsy surgery” at &lt;3 between August 2006 and February 2019 at the National Center of Neurology and Psychiatry, Tokyo, Japan ≥1 year follow-up postoperative, and post-operative developmental assessment at 1 year or last follow-up after 2 years or longer. Excluded patients who had undergoing palliative procedures (corpus callosotomy and vagus nerve stimulation implantation).</td>
<td>22 hemimegalencephaly, 33 other malformations of cortical development, 10 low-grade developmental tumors, 6 tuberous sclerosis complex, 3 Surge-Weber syndrome, 1 perinatal ischemia.</td>
<td>Mortality (patients required to have ≥1 year follow-up after surgery) Hydrocephalus requiring surgical intervention (NR)</td>
<td></td>
</tr>
<tr>
<td><strong>Steinbok et al. 2009</strong>&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Lesionectomy, cortical resection, and hemispheric surgery (n = 151 procedures in 116 patients)</td>
<td>Age &lt;3 years undergoing epilepsy surgery at multiple centers across Canada from January 1987 to September 2005. Patients undergoing surgery for a lesion, such as a tumor, who happened to present with seizures but for whom the surgery was performed for the lesion rather than the epilepsy were excluded.</td>
<td>NR by procedure</td>
<td>Mortality (intraoperative) Hydrocephalus (within a “few months” after surgery) Other AEs</td>
<td></td>
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Abbreviations: FCD = focal cortical dysplasia; HME = hemimegalencephaly.

Nine infants reported in Iwasaki 2021<sup>26</sup> had previously been reported in Otsuki et al. 2013. For Steinbok et al.<sup>26</sup> the number of hemispheric vs nonhemispheric procedures for which hydrocephalus was reported was unclear.
Only 3 retrospective chart reviews reported data for infants undergoing anatomical hemispherectomy. Cook et al. reported of 14 infants: there was 1 intraoperative death, an 8-month-old infant with HME. Two additional studies with 12 infants reported no deaths. Evidence was insufficient to permit conclusions because of sparse data.

Eight studies described surgical mortality for a combined 196 infants undergoing functional hemispherectomy/hemispherotomy. Seven of 8 studies (including 180 infants) reported no deaths. Kumar et al. reported of 16 hemispherotomies, 1 death occurred in an infant with epidermal nevus syndrome, right HME, and multiple other congenital abnormalities who developed refractory seizures after surgery and technological support was withdrawn.

Steinbok et al. reported a single death across 116 infants undergoing 151 surgical procedures (hemispherectomy/hemispherotomy, lesionectomy, or cortical resections). The intraoperative death occurred in a 3.9 months child with tuberous sclerosis undergoing attempted resection of intraventricular and extraventricular lesions.

Overall, these studies suggest perioperative mortality after functional hemispherectomy or hemispherotomy is uncommon. However, these studies were primarily single center retrospective chart reviews including heterogenous infants (with many different seizure etiologies), and studies often failed to specify the proportion of infants not included because of missing data. Furthermore, it is possible that centers with higher mortality rates might choose not to publish their data. However, despite these study limitations, we concluded surgical mortality after functional hemispherectomy/hemispherotomy is rare (SOE: Low).

**Hydrocephalus**

For anatomical hemispherectomy, 3 studies (combined 19 surgeries) reported hydrocephalus and/or need for a ventriculoperitoneal shunt (VPS) were common. Dunkley et al. reported 2/2 infants undergoing anatomical hemispherectomy required VP shunt placement 12 months after surgery. Similarly, Pinto et al. reported 7/10 infants undergoing anatomical hemispherectomy required VP shunt placement (follow-up interval NR). Lettori et al. reported 3/7 infants undergoing anatomical hemispherectomy or hemidecortication developed hydrocephalus (follow-up interval NR).

For functional hemispherectomy or hemispherotomy, 9 studies (combined n = 96, plus infants from 1 study only reporting a percentage, and another study with an unclear denominator) reported on hydrocephalus. Studies reported lower rates of hydrocephalus/VPS compared with anatomical hemispherectomy. One of 9 studies reported no infants (0/10) developed hydrocephalus. Another study reported 4 infants undergoing functional hemispherectomy developed hydrocephalus within a few months after surgery; at least 22 infants underwent functional hemispherotomy in this study, but the total number of infants undergoing this procedure was unclear. The remaining 7 studies reported rates of 8% (1/12), 11% (3/27), 16% (n NR), 20% (1/5), 22% (6/27), 25% (4/16), and 33% (1/3).

Finally, Roth et al. reported hydrocephalus in 25% (11 of 44) infants undergoing either anatomical hemispherectomy or functional hemispherectomy/hemispherotomy. Notably, only 1 study reported when hydrocephalus occurred, although a second study reported a time range. Four studies did not report when hydrocephalus occurred, and the remaining studies provided a time point at which other outcomes were measured (e.g., >1 year after surgery) but no other information regarding the timing of hydrocephalus.

Given multiple factors including heterogeneity across patients and procedures and inconsistent outcome reporting, evidence was deemed insufficient to draw a conclusion regarding hydrocephalus and/or VPS after hemispherectomy/hemispherotomy.

**Multilobar, Lobar, and Focal Resections**

**Mortality**

Four pre-studies/poststudies described surgical mortality for infants undergoing nonhemispheric procedures. Three studies described surgical mortality for a combined 82 infants undergoing multilobar, lobar, or focal resections and reported no deaths. These 3 studies included infants undergoing a range of nonhemispheric procedures. Dunkley et al. included 15 infants undergoing either multilobar, lobar, or focal resections. Iwasaki et al. included 48 infants undergoing multilobar (13 posterior quadrantical disconnections, 5 multifocal cortical resections, 1 subtotal hemispherotomy) or unilobar surgeries (16 focal cortical resections or lesionectomies, 8 anterior temporal lobectomies, and 5 frontal lobectomies or disconnections). Roth et al. included 19 infants undergoing focal resections.

A fourth study, Steinbok et al. reported only a single mortality across 116 infants undergoing 151 procedures, which were either a hemispherectomy/hemispherotomy, lesionectomy, or cortical resections.

This evidence base for mortality after nonhemispheric procedures is small with important limitations. All studies were retrospective chart reviews, and 2 studies reported experience drawn from single centers. However, the results from Roth et al. (which included data from 19 centers) were consistent in also reporting no deaths. Reported mortality rates may be artificially low if centers with higher mortality rates choose not to publish their data. Nevertheless, despite these limitations, we concluded surgical mortality after multilobar, lobar, or focal resection is rare (SOE: Low).

**Hydrocephalus**

Four studies with a combined 108 procedures reported on infants undergoing focal, intralobar, or multilobar resections. No patients developed hydrocephalus (follow-up duration NR for 2 studies, median of 24 months, and >1
year after surgery\textsuperscript{36}). Despite study limitations, we concluded that hydrocephalus after multilobar, intralobar, or focal surgery is rare (SOE: Low).

**Additional Adverse Effects (All Procedures)**

Reporting of other AEs was inconsistent. Two studies\textsuperscript{26,29} reported other AEs after anatomic hemispherectomy including infection, transient fever, cranial nerve III palsy, subdural fluid collection, and CSF leakage. For functional hemispherectomy/hemispherotomy, in addition to infection,\textsuperscript{26,29} AEs reported included intraoperative disseminated intravascular coagulation (1/37),\textsuperscript{28} acute postsurgical seizures (23%),\textsuperscript{19} epidural hemorrhage requiring surgical revision (1/22),\textsuperscript{19} dural adhesions requiring late reoperation (1/41),\textsuperscript{29} pituitary failure because of thalamic lesion (1/22),\textsuperscript{19} cerebral salt wasting syndrome (2/27),\textsuperscript{36} diabetes insipidus (3/27),\textsuperscript{36} sinus thrombosis resulting from diabetes insipidus (2/27),\textsuperscript{36} and asymptomatic hemorrhagic infarction (1/27).\textsuperscript{36}

For multilobar, lobar, or focal resections, 1 study reported 1/10 infants developed transient hemiparesis after posterior disconnection for refractory posterior quadrant epilepsy.\textsuperscript{21} Another study\textsuperscript{36} reported the following complications requiring surgical or medical intervention in 48 infants undergoing multilobar, unilobar, or focal resections: subdural hygroma (n = 3), cyst formation (n = 2), asymptomatic cerebral infarction (n = 1), bacterial meningitis (n = 1), and psychiatric symptoms (n = 1).

**Discussion**

Our findings suggest surgical interventions for children aged 1–36 months with epilepsy can be beneficial for reducing seizures for some children, and surgical mortality is rare. Although other outcomes including developmental/cognitive outcomes, sleep, and QOL are also important, few or no studies reported these. Overall, the evidence base remains sparse, with key limitations, including a lack of prospective controlled studies, and inadequate measurement of important outcomes. Despite including studies reporting as few as 10 patients per procedure, we identified only 18 studies, of which all were prestudies/poststudies and 17 were retrospective. Notably, the absence of rigorous trials in this age group does not demonstrate that surgery is ineffective, instead it highlights a critical evidence gap.

Despite these limitations, the rates of seizure freedom for infants undergoing hemispherectomy/hemispherotomy or other resections (multilobar, lobar, or focal resections) reported in studies were encouraging. For hemispherectomy/hemispherotomy, with 1 exception, studies reported more than half of infants were seizure free at follow-up. Similarly, for multilobar/lobar/focal resections, studies reported seizure freedom rates of 40%–70%. Furthermore, we found low strength evidence suggesting surgical mortality was rare. As seizure freedom rates with medical management in children 1–36 months old with DRE are substantially lower than 40%–70%, these findings suggest epilepsy surgery can be beneficial for treating seizures in this age group.

Some studies reported on surgeries performed 4 decades ago, raising questions regarding generalizability, given the changes in clinical care over time. However, most studies reported seizure freedom rates similar to those reported by Roth\textsuperscript{28} (56% and 70% for focal and hemispheric procedures, respectively) a larger recent study which included patients from multiple centers operated on from 1999 to 2020. A recent study (published subsequent to our search dates) reported of 34 children <3 undergoing epilepsy surgery since 2018, 59% were Engel I outcome at median follow-up of 21.9 months.\textsuperscript{37}

Several factors may limit applicability of these findings. Ideally, outcomes after surgery would be reported by etiology, given the wide range of etiologies with unique clinical considerations and trajectories that may lead to DRE and evaluation for epilepsy surgery. However, sparsity of studies, clinical heterogeneity of included patients, and limitations of study reporting precluded this type of assessment. Limited reporting of clinical details also precluded consideration of other clinical factors (e.g., the number of ASM at outcome reporting, number of previous surgeries, variation in surgical procedures) on outcomes.

Most studies were small and single center, reflecting outcomes from single epilepsy surgery programs and/or surgeons. Furthermore, nearly all studies were retrospective chart reviews at risk for inconsistencies in data collection and reporting. One study of consecutive infants included only <50% (24/50) of potentially eligible infants because of missing data,\textsuperscript{32} illustrating the potential for bias from studies using a retrospective chart review design. However, few studies reported the proportion of patients excluded because of missing data. Although only studies published after 1999 were included, surgeries described were performed over 4 decades. Although excluding studies published before 1999 could have excluded relevant data, including older studies could also have resulted in inclusion of even older and potentially less generalizable data.

Although we found existing evidence to be sparse and low quality, notably, the lack of high quality studies does not demonstrate that surgical treatments are ineffective. Instead, it highlights the need for additional higher quality evidence. The scope of our review was limited to children aged 1–36 months because of AES’s request to focus on this particular population, feasibility considerations, and resources. Although exploration of indirect evidence (e.g., studies performed in older children) could provide useful information, this was not feasible given resource constraints.

To improve the SOE, improvements to study design and data reporting are needed. In 2012, an Institute of Medicine report named long-term prospective studies assessing effects of epilepsy surgery on cognitive function with inclusion of appropriate control groups as a research priority.\textsuperscript{38} Our findings demonstrate this remains an evidence gap for surgical treatments in early life epilepsy. Prospective studies with clear and consistent reporting of variables including seizure etiology,
seminology, previous and concomitant treatments, and follow-up interval are needed. As others have noted, seizure freedom remains challenging to define and key differences between the Engel classification and ILAE outcome scales pose challenges for comparing results from studies using these scales.39

Pragmatic and ethical concerns exist regarding randomizing infants with epilepsy to surgery vs sham or placebo. However, a feasible next step would be a high-quality prospective, multicenter observational cohort study. This could be facilitated by a multicenter registry with standardized measures (including developmental outcomes, QOL outcomes, and adverse effects). This type of registry would offer important advantages: 1) given the relatively small number of infants undergoing surgical interventions, gathering data across multiple centers would increase the ability to measure efficacy/harms and avoid potential duplicate reporting of patients in studies, 2) improve generalizability by minimizing differences specific to individual institutions or surgeons, 3) facilitate consensus about outcome measurement (including key outcomes and follow-up duration), and 4) provide a framework for prospective efficient collection of standardized data.40 Existing consortiums could play a role in facilitating development.

Development of core outcomes specific to patients with early life epilepsy could also support these efforts. Outcomes identified as important by stakeholders interviewed during protocol development including seizure freedom, seizure frequency, seizure severity, Engel classification, all-cause mortality, hospitalization, neurodevelopmental outcomes, QOL, sleep quality, caregiver QOL, treatment cost, and other adverse events. Given the range of seizure etiologies and surgical interventions, future studies should not only report these outcomes but also report outcomes separately for different seizure etiologies (i.e., structural vs acquired) and surgeries (i.e., focal cortical resection vs frontal lobectomy). Even some structural lesions may be further divided by detailed pathologic assessments or genetic etiologies. Without this information, future systematic reviews are likely to encounter similar difficulty drawing conclusions about specific etiologies or procedures in this age group.

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Appendix

Appendix Authors

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<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
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<tbody>
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References


Surgical Treatments for Epilepsies in Children Aged 1–36 Months: A Systematic Review
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