RESEARCH ARTICLE

Diagnosis and Management of Adult Status Epilepticus in Resource-Limited Settings

A Systematic Review

Aayesha J. Soni,[1] R. Grace Couper,[2] M. Pilar Vicuna,[1] and Jorge G. Burneo[1,2]

Neurology® 2025;104:e213479. doi:10.1212/WNL.0000000000213479

Correspondence
Dr. Soni
ajsoni008@gmail.com

MORE ONLINE

Supplementary Material

Abstract

Background and Objectives

Status epilepticus (SE) is the leading cause of death in patients with epilepsy, and it affects people in low/middle-income countries (LMICs) at a much higher rate. There is likely a significant gap between the recommended diagnosis and treatment of SE and current practices in resource-limited settings. We conducted a systematic literature review to determine how convulsive and nonconvulsive SE in adults is diagnosed and managed in LMICs.

Methods

All relevant articles from Embase, Medline, PubMed, and the Virtual Health Library Regional Portal databases, published before September 16, 2024, were included. Studies needed to take place in LMICs and include treatment and outcomes of patients with SE. This review followed the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines. The risk of bias was assessed using the Risk of Bias in Randomized Trials and Risk of Bias in Non-randomized Studies of Interventions tools.

Results

Our review included 23 studies from 3 continents including 1,526 patients, with most of the studies conducted in Asia. There is a lack of literature from Africa and surrounding the topic of nonconvulsive SE. The commonest etiology of SE was an acute symptomatic cause (21%–88%), with encephalitis predominating overall. Diagnostic and management practices varied greatly, dictated by local availability of drugs and expertise, rather than guidelines. First-line benzodiazepines were routinely underdosed while older and cheaper second-line antiseizure medications, such as valproic acid, phenytoin, and phenobarbital, were more frequently administered. In addition, there was a general lack of access to continuous EEG monitoring, with only 5 studies from tertiary-level centers in Asia reporting its usage. Mortality outcomes of up to 42.6% are higher in comparison with high-income countries.

Discussion

The heterogeneity in management practices of SE in LMICs highlights the lack of consistent treatment, with very few studies from Africa and Latin America available in the literature. This contributed to the limitations of this review, with only a small region of countries (mostly from Asia) represented and retrospective review of clinical records predominantly used. The non-uniformity of diagnostic and management practices in SE has highlighted the need for clinically appropriate guidelines in LMICs.

Introduction

Status epilepticus (SE) is a neurologic emergency that requires timely treatment.[1] While the prevalence of epilepsy is reported to be higher in Africa, Latin America, and other low/middle-

[1]Epilepsy Program, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada; and [2]Neuroepidemiology Research Unit, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada.

Glossary

AS = acute symptomatic; **ASM** = antiseizure medication; **BZD** = benzodiazepine; **cEEG** = continuous EEG; **CSE** = convulsive SE; **ESETT** = Established Status Epilepticus Treatment Trial; **HIC** = high-income country; **LEV** = levetiracetam; **LMIC** = low/middle-income country; **mRS** = modified Rankin scale; **NCC** = neurocysticercosis; **NCSE** = nonconvulsive SE; **PB** = phenobarbital; **PHT** = phenytoin; **PWE** = persons with epilepsy; **RCT** = randomized controlled trial; **SE** = status epilepticus; **TG** = treatment gap; **TPM** = topiramate; **VPA** = valproic acid.

income countries (LMICs) with approximately 80% of persons with epilepsy (PWE) worldwide living in these regions,[2] so too is the incidence of SE, although epidemiologic data are scarce.[3] Mortality in PWE of LMICs is higher than in high-income countries (HICs) and is estimated to be 2.6-fold higher than in general populations of LMICs, with SE as one of the main causes.[4]

In LMICs, optimal management of SE is associated with major barriers: (1) poor health care infrastructure and clinical training; (2) lack of access to health care centers, with poor connectivity and delays in transportation; (3) intermittent availability of drugs; and (4) lack of economic affordability.[5] Furthermore, while the spotlight is often on convulsive SE (CSE), nonconvulsive subtypes of SE (NCSE) are even more difficult to characterize without readily available access to EEG, especially in areas such as Sub-Saharan Africa.[6]

The treatment gap (TG) of SE is well recognized,[3] defined conceptually as the proportion of PWE who do not receive appropriate, comprehensive treatment of the total number of PWE in a population.[7] The TG is more than 75% in LMICs, compared with less than 10% in HICs,[8] and there are few proposed solutions published to address this. The absence of trained physicians was an important contributing factor to the TG in Asia.[3] Although it would be ideal for all SE cases to be managed by a neurologist, there are significantly lower numbers of specialists serving populations in LMICs in general.[6] Interventions need to be aimed at primary health care and prehospital personnel. To propose solutions, the extent of the problem first needs to be assessed.

We conducted a systematic review to assess how SE is currently diagnosed and managed in LMICs and to identify whether management is in line with current international guidelines and protocols.

Methods

Search Strategy

A systematic search strategy was used to find literature on the management of SE in LMICs. Articles were extracted from Embase, Medline, PubMed, and the Virtual Health Library Regional Portal (including WPRIM [Western Pacific], LILACS, IBECS, BINACIS, CUMED, LIPECS, AIM, BIGG-GRADE guidelines, and VETINDEX) databases on September 16, 2024 (eMethods). Search terms used and adapted for each database were as follows: (status epilepticus) OR (convulsive OR nonconvulsive status epilepticus) OR (refractory status epilepticus) OR (super refractory status epilepticus) AND (low OR middle OR poor OR limited) AND (resource OR income OR developing countries) AND (treatment OR management). We included randomized controlled trials (RCTs), nonrandomized clinical trials, case series, case-control studies, cohort studies, and cross-sectional studies in the initial search and excluded case reports, editorials, commentary letters, replies to editors, book reviews, non–peer-reviewed articles, conference proceedings, poster abstracts, and dissertations for the final selection.

Review Protocol

The implementation and reporting of this systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. During the initial manual screening, titles and abstracts were independently assessed by 2 reviewers to determine inclusion or exclusion. The reviewers (A.J.S. and R.G.C.) used Covidence systematic review software for the process and were blinded to each other's evaluations. A third reviewer (J.G.B.) helped decide on all discrepancies or cases where a reviewer was uncertain. Subsequently, all included articles underwent a full-text review by A.J.S. and R.G.C.

Inclusion and Exclusion Criteria

A standardized set of inclusion and exclusion criteria was applied during the title/abstract and full-text review stages. Inclusion criteria included articles that examined the diagnosis and treatment of SE in LMICs, using the World Bank (2022 data) to define LMICs. Included studies provided details of specific treatments and at least 1 outcome including termination of SE, progression to refractory or super refractory SE, modified Rankin Scale (mRS) score, or death at discharge or follow-up within 1 year of discharge. Exclusion criteria included articles missing details of patients treated for SE, lacking treatment details or with no single outcome measure, involving participants younger than 16 years, using animal subjects, or with excluded study types (eMethods). However, these studies were still reviewed to identify potential articles not found in the initial search. In studies where samples included pediatric patients younger than 16 years, the authors were contacted to obtain specific information for adult patients, which could be included in the review. In the event of no response or inability to contact the authors through the contact information provided, the studies were excluded. Articles written in languages other than English were not

excluded. Instead, these texts were translated into English to assess for suitability. Considering the limited body of literature and the methodological variations present in the published studies, demographic factors (apart from age), study-specific inclusion/exclusion criteria, SE and NCSE diagnostic criteria, presence or absence of specific comorbidities assessed in certain groups, and selected missing details of specific treatments at each SE step were not used as grounds for exclusion. Nonetheless, this information was gathered and reported whenever it was available.

Quality Assessment

Two reviewers (A.J.S. and R.G.C.) assessed the risk of bias independently. The Risk of Bias in Randomized Trials tool was used for RCTs, and the Risk of Bias in Non-randomized Studies of Interventions tool for nonrandomized studies with interventions was used for the remaining studies.

Data Extraction

Data extraction was independently performed by 2 of the authors (A.J.S. and R.G.C.), using a custom-designed data extraction form. In cases of disagreement, 3 authors (A.J.S., R.G.C., and J.G.B.) discussed the discrepancies to reach a consensus. The information extracted included first author, year and country of study, study design, total sample size, patient ages and sexes, and etiology of SE as per International League Against Epilepsy guidelines, as well as the subgroups if specified (acute symptomatic [AS], remote symptomatic, progressive symptomatic, cryptogenic, noncompliance to antiseizure medications [ASMs]), type of SE (convulsive, nonconvulsive) at onset, time variables (including time to medical attention and time to abort seizures), and diagnostics used, which were classified as clinical only, clinical and routine EEG, clinical and continuous EEG, or unknown access to EEG. Intervention details such as medication and dose were collected according to different groups of drugs used to treat SE. They were classified as benzodiazepines (BZDs) typically used as first-line treatment, ASMs, anesthetic drugs, and additional treatment. Any outcome measure at discharge or up to 1-year after discharge was recorded.

Standard Protocol Approvals, Registrations, and Patient Consents

This systematic review was not registered. Patient consent is not required for a systematic review.

Data Availability

All data pertaining to this work (list of abstracts, articles reviewed, data entry spreadsheet, and statistical analysis) will be made available on request by any qualified investigator.

Results

Search Results

The literature search yielded 2,008 individual citations related to SE in LMICs. Although 236 citations passed title and abstract screening, only 23 met the eligibility criteria and were included in this review (Figure 1).

Study Characteristics

The designs of included studies were case series, nonrandomized clinical trials, retrospective cohort studies, cross-sectional studies, and RCTs. Study designs were classified using Cochrane's Effective Practice and Organization of Care classification. Most studies were conducted in Asia while 1 study was conducted in Africa and 3 in Latin America. Sample sizes ranged from 8 to 313 (total of 1,526) patients with SE. Only 2 studies[9,10] included patients with NCSE exclusively, both with small sample sizes of 12 and 14 patients, while 5 other studies assessed patients with CSE or NCSE. One study included only women[11] while all other studies included men and women. Two studies potentially included the same patients in both study populations because the same researchers conducted the studies in overlapping time frames.[12,13] Additional study characteristics are summarized in Table 1.

Study Findings

The main study findings are summarized in Tables 2 and 3, and detailed results are discussed further.

Quality of Studies

The risk of bias is presented in Figure 2. All studies had a moderate or high risk of bias.

Etiology of SE

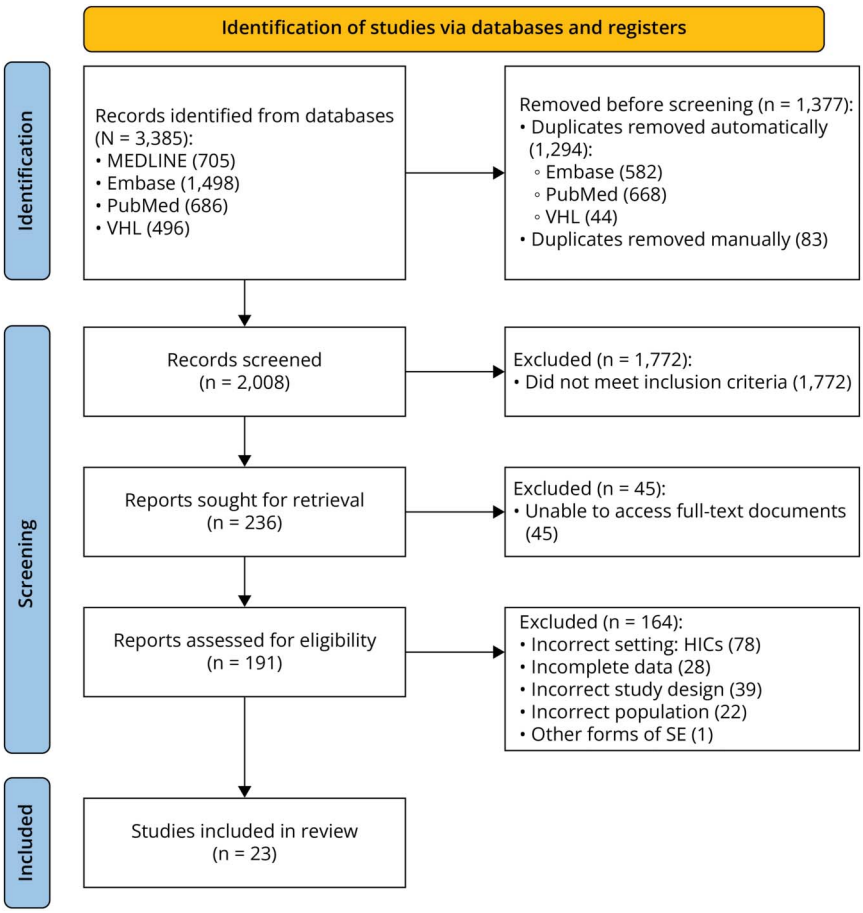
An AS etiology was the most common cause of SE in LMICs. Although some studies only included patients with a specific AS etiology, such as infection or stroke, most included patients with any etiology. Studies that included multiple etiologies of SE reported an AS etiology in 21.4%[14]–88.2%[11] of patients. Noncompliance to ASMs was another common etiology of SE in LMICs, as seen in 0%–54% of patients. Other reported etiologies included remote symptomatic, progressive symptomatic, cryptogenic, epilepsy-related, and other/unknown (Figure 3).

Time to Medical Attention

Most studies did not report the time to receive medical attention or abort seizures. Those that reported time to medical attention indicated a range from 2 minutes[15] to more than 24 hours.[16] Similarly, studies that reported the time to abort seizures indicated a range from 1 minute[17] to 1 week.[12] Few studies reported time to medical attention or abort seizures of less than 1 hour.[13,15,16,18]

Studies that assessed the association between SE duration and outcomes reported mixed results. A study conducted in India[19] found that time to control seizures longer than 3.5 hours was associated with a higher risk of death or loss of cortical function while 2 other studies[11,20] found that a delay in treatment was not associated with mortality. However, 2 studies[13,20] found a short duration of SE was associated with a better response to first-line treatment. By contrast, a study from India[21] found no association between the duration of SE and refractoriness.

Figure 1 PRISMA Flowchart



PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analyses; SE = status epilepticus; VHL = Virtual Health Library.

Diagnostics Used for SE

In addition to clinical data used to diagnose SE in all studies, continuous EEG (cEEG) was only used in 5 studies, all conducted in Asia in tertiary-level health care centers. In 9 studies, routine EEG was used in at least some patients, and 9 studies were unclear or did not mention the use of EEG. Of interest, one of the studies from the Philippines[9] that assessed only patients with NCSE did not have access to cEEG, relying mostly on periodic routine EEGs and clinical assessments.

Benzodiazepine Use as First-Line Treatment

In 15 of 23 studies, BZDs were given to all patients as the first-line treatment, either alone or in combination with another ASM (most commonly phenytoin [PHT]). In 7 studies, only some patients were given BZDs, and BZD use was not documented at all in one study.[17] IV diazepam was the only BZD used in 8 studies, IV lorazepam in 5 studies, IV midazolam in 1 study, and oral clonazepam in one study,[10] and the remaining studies used multiple types of BZDs (Figure 4). In only 1 study were patients administered more than 1 BZD concurrently.[22]

IV diazepam was administered ranging in doses from 0.1 to 0.2 mg/kg[18,19,23,24] (inconsistently repeated once or twice if SE was not successfully aborted), to single 5–30 mg doses.[15,16,24] The second most commonly used BZD, IV lorazepam, was consistently administered at 0.1 mg/kg.[12,13,21,24] Response to first-line treatment was found to be associated with a lower risk of mortality in 1 study.[12]

ASMs Used as Second-Line Treatment

The most common ASM used to treat SE was valproic acid (VPA), used in 18 of 22 studies in at least some patients. Where doses were provided, 20–30 mg/kg or 0.4–2 g/d of IV VPA was often given. Other common ASMs were levetiracetam (LEV) administered intravenously or orally in doses of 20–40 mg/kg or 0.5–3 g/d in 13 studies, PHT given in doses of 18–20 mg/kg or 0.3–1.6 g/d in 12 studies, and phenobarbital (PB) as IM or IV in doses of 18–20 mg/kg or 0.3–0.6 mg/d. Of interest, oral ASMs were not uncommonly used, with topiramate (TPM) seen most frequently and studies from Turkey,[10] India,[20,25] and China[17] administering a wide range of other oral ASMs including carbamazepine, oxcarbazepine, clobazam, and clonazepam. Owing to the wide and varied use of ASMs, conclusions could unfortunately not be drawn concerning ASM choice and outcome measures.

Among RCTs, 2 studies demonstrated at least some benefits of using PB over VPA.[23,26] Among patients refractory to diazepam, those who received PB were more likely to have SE

Table 1 Characteristics of Included Studies

Study	Country	Study design	Sample size	Sexes	Age (y) Mean ± SD or mean/range or median (range)
Africa					
Bechri (2023)[29]	Morocco	Case series	82	50 M 32 F	39.5 (18–95)
Asia					
Amiri-Nikpour (2018)[27]	Iran	RCT	110	51 M 59 F	42.9 ± 16.7
Andal (2020)[9]	Philippines	Case series	14	6 M 8 F	52 (22–77)
Asadi-Pooya (2015)[15]	Iran	Nonrandomized clinical trial	20	14 M 6 F	44.5 ± 23.2
Dani (2019)[19]	India	Case series	55	36 M 19 F	39.1 ± 15.3
Dericioglu (2014)[10]	Turkey	Case series	12	9 M 3 F	58 (24–86)
Kalita (2016)[50]	India	Case series	10	3 M 7 F	34 (18–71)
Kalita (2024)[25]	India	Case series	8	4 M 4 F	27 ± 12.7
Li (2014)[17]	China	Case series	13	8 M 5 F	23 (16–60)
Liu (2023)[23]	China	RCT	98	54 M 44 F	42.5 ± 17.8
Misra (2008)[21]	India	Case series	37	20 M 17 F	37 (16–78)
Nene (2019)[28]	India	RCT	118 (100 completed)	79 M 46 F	67.5 ± 7.5
Ozdemir (2015)[19]	Turkey	Case series	17	7 M 10 F	71.2 ± 11.5
Ozdilek (2013)[20]	Turkey	Case series	88 (101 episodes)	47 M 41 F	32/16–50
Peng (2023)[16]	China	Retrospective cohort	313	186 M 127 F	43 (16–92)
Quintay (2023)[45]	Philippines	Case series	61	30 M 31 F	53.3 ± 18.3
Rajiv (2017)[11]	India	Case series	17	17 F	23.7 ± 3.0
Su (2021)[26]	China	RCT	69	42 M 27 F	43 ± 20
Verma (2019)[12]	India	Case series	162	73 M 40 F	41.7 ± 19.7
Verma (2022)[13]	India	Cross-sectional	122	97 M 25 F	67.1 ± 7.7
Latin America					
Bedoya-Sommerkamp (2021)[22]	Peru	Case series	59	37 M 22 F	47 (18–92)
De la Cruz (2014)[14]	Peru	Case series	28	16 M 12 F	31 (18–68)
Skinner (2010)[18]	Honduras	Case series	31	13 M 18 F	35.1 ± 13.3

Abbreviations: F = females; M = males; RCT = randomized controlled trial.

Table 2 ASM Treatment and Outcomes of Nonrandomized Studies

Study	No. of ASMs	ASM type (route; dose [if reported])		Outcomes
Andal (2020)[9]	0: 8 1: 3 2: 3	4 LEV (PO) 5 VPA (IV)		Death: 5 mRS (0–2): 3 mRS (3–5): 6
Asadi-Pooya (2015)[15]	2: 10 3: 10	20 PHT (IV; 1,200–1,600 mg) 20 TPM (EN; 400 mg then 200 mg BID)	6 PBT (IV) 4 VPA (IV)	Death: 7 mRS (0–2): 11 mRS (3–5): 2
Bechri (2023)[29]	0: 3 1: 79	79 PBT (IV)		Death: 31 Recovery (NS): 51
Bedoya-Sommerkamp (2021)[22]	0:42 1: 17	17 PHT (IV) *Patients received PHT instead of BZDs		Death: 5 mRS (0–2): 37 mRS (3–5): 17
Dani (2019)[19]	1: 41 2: 14	46 FOS (IV) 8 LEV (IV) 1 VPA (IV)		Death or loss of cortical function: 20 Favorable (NS): 35
De la Cruz (2014)[14]	0: 2 1: 26	24 PHT (IV) 2 PBT (IV)		At 30 d (20 completed): Death: 0 Poor outcome: 3
Dericioglu (2014)[10]	1: 1 2: 4 3: 3 4: 3 5: 1	11 LEV (IV) 9 PHT (IV) 1 PBT (IV) 7 TPM (PO)	2 VPA (IV) 2 CBZ (PO) 2 OXC (PO)	Death: 4 mRS (0–2): 6 mRS (3–5) 2
Kalita (2016)[50]	1: 6 2: 4	7 LEV (IV; 30 mg/kg) 2 PHT (IV; 20 mg/kg) 3 VPA (unknown)	1 LAC (unknown) 1 CLOB (unknown)	mRS (0–2): 7 mRS (3–5): 3
Kalita (2024)[25]	1: 1 2: 4 3: 1 4: 1	5 LEV (IV) 2 LAC (IV) 1 VPA (IV)	4 CLOB (PO) 1 CLON (PO) 1 OXC (PO)	Death: 3 mRS (0–2): 2 mRS (3–5): 3
Li (2014)[17]	2: 3 3: 3 4: 5 5: 2	12 VPA (IV; 0.5–2 g/d) 9 PBT (IV; 0.3–0.6 g/d) 8 TPM (PO; 50–100 mg/d) 8 LEV (IV; 1–3 g/d)	3 OXC (PO; 0.6–0.9 g/d) 2 CLON (PO; 2–4 mg/d) 1 PHT (IV; 0.3 g/d) 1 CBZ (PO; 0.3–0.6 g/d)	Death: 2
Misra (2008)[21]	1: 25 2: 8 >2: 4	18 VPA (IV; 30 mg/kg) 19 PHT (IV; 20 mg/kg) 2 CBZ (PO)	1 CLOB (PO) 1 GAB (PO)	Death: 13 (29.7%)
Ozdemir (2015)[24]	1: 17	VPA: 17 (IV; 20 mg/kg then 400 mg TID)		Refractory to ASM: 5 Death: 2 mRS (0–2): 5 mRS (3–5): 10

Continued

Table 2 ASM Treatment and Outcomes of Nonrandomized Studies *(continued)*

Study	No. of ASMs	ASM type (route; dose [if reported])		Outcomes
Ozdilek (2013)[19]	unclear	Unclear PHT (IV; 18 mg/kg + 10 mg/kg if needed) Unclear PBT (IV; 18 mg/kg + 10 mg/kg if needed)		Death: 12 Not documented: 13
Peng (2023)[16]	None: 194 1: 119 (82 as first treatment)	38 PBT (IM; 100 mg) 70 VPA (IV; 400–1,200 mg/d or 16–200 mg/h) 2 LEV (IV; 500 mg)	2 LEV (PO; 0.5–1 g) 7 Unclear	Death: 12 (6 with BZD group, 6 non-BZD) Fail to control after first treatment: 72.4% BZD, 44.1% non-BZD
Quintay (2023)[45]	≥1: 61	LEV (IV; 0.5–2 g) and/or VPA (IV; 0.5–2 g)		Death: 26
Rajiv (2017)[11]	1: 5 2: 12	12 FOS (IV) 9 PBT (IV)	4 LEV (IV) 2 VPA (IV)	Refractory to treatment: 10 Death: 0 mRS (0–2): 13 mRS (3–5): 4
Skinner (2010)[18]	1: 13 >1: 17	29 PHT (IV) Unclear CLON (PO)		Death: 4
Verma (2019)[12]	1: 133 2: 29	162 PHT (IV; 20 mg/kg) 29 VPA (IV; 25–30 mg/kg) or LEV (IV; 40 mg/kg)		Death: 6
Verma (2022)[13]	≥1: 122	122 PHT (IV; 20 mg/kg) N/R VPA (IV) or LEV (IV)		Death: 32

Abbreviations: ASM = antiseizure medication; BZD = benzodiazepine; CBZ = carbamazepine; CLOB = clobazam; CLON = clonazepam; DEX = dexmedetomidine; DIAZ = diazepam; EN = enteral; FENT = fentanyl; FOS = fosphenytoin; GAB = gabapentin; KET = ketamine; LAC = lacosamide; LEV = levetiracetam; LOR = lorazepam; MID = midazolam; mRS = modified Rankin Scale; N/A = not applicable; NS = not specified; OXC = oxcarbazepine; PBT = phenobarbital; PHT = phenytoin; PROP = propofol; TPM = topiramate; VPA = valproic acid.

Table 3 ASM Treatment and Outcomes for RCT

Study	Patient details	No. of ASMs	ASM type (route; dose [if reported])	Outcomes
Amiri-Nikpour (2018)[27]	Patients suffering from BZD-refractory SE, randomized to PHT or VPA	1: 110	55 PHT (IV; 20 mg/kg then 1.5 mg/kg TID) 55 VPA (IV; 30 mg/kg then 4–8 mg/kg TID)	Response to first ASM: 43 VPA; 39 PHT Death (at 7 d): 14 (7 PHT, 7 VPA) No significant differences between ASMs
Liu (2023)[23]	Patients with SE refractory to diazepam treatment, randomized to PBT or VPA	1: 98	50 PBT (IV; 20 mg/kg + 10 mg/kg if needed) 48 VPA (IV; 30 mg/kg + 15 mg/kg if needed)	At 3 mo: Death: 21 (8 PBT, 13 VPA) mRS (0–2): 45 mRS (3–5): 32 At 12 mo, PBT had better outcomes, no difference in mortality
Nene (2019)[28]	Patients with SE randomized to receive VPA or LEV immediately after administering LOR	1: 81 2: 19	50 VPA (IV; 20–25 mg/kg then 20–25 mg/kg/d) 50 LEV (IV; 20–25 mg/kg then 20–25 mg/kg/d)	Response to first ASM: 81 (38 VPA, 42 LEV) mRS (0–3): 67 mRS (4–6): 33 No significant differences between ASMs
Su (2021)[26]	Patients with SE with no response to first-line treatment (DIAZ) randomized to VPA or PBT	1: 69	33 PBT (IV; 20 mg/kg + 10 mg/kg if needed) 36 VPA (IV; 30 mg/kg + 15 mg/kg if needed)	28/33 PBT—SE responded in 1 h 23/36 VPA—SE responded in 1 h Death: 5 (2 PBT, 3 VPA) PBT had significantly more responders

Abbreviations: ASM = antiseizure medication; BZD = benzodiazepine; DIAZ = diazepam; LEV = levetiracetam; LOR = lorazepam; mRS = modified Rankin Scale; PBT = phenobarbital; PHT = phenytoin; RCT = randomized controlled trial; SE = status epilepticus; VPA = valproic acid.

termination within 1 hour and had better outcomes at 1 year (excluding death).[26] The other 2 RCTs found no significant difference in outcomes in patients randomized to VPA and PHT[27] or LEV[28] (Table 3).

Outcome Measures

Nineteen studies reported an outcome of death, ranging in time from in-hospital to 1 year later. Other outcomes included termination of seizures, progression to refractory SE, relapses or recovery of SE, and mRS scores. Death was reported in 0%–42.6% of patients, although patient characteristics were heterogeneous across studies regarding age, comorbidities, and etiologies. A poor mRS score was seen in a similar proportion of patients across studies, with 10%–58.8% having an mRS score of 3–5. An increased risk of mortality was associated with refractory or uncontrolled SE,[21,28] and 30-day mortality was associated with a poorer mRS score at discharge.[28]

One of the larger included studies[28] identified an AS etiology associated with a poorer outcome. This was a common etiology in other included studies as well, which could be a possible correlate with our higher reported mortality rates. However, this was not uniform or estimated. Another included study only found patients aged older than 70 years[20] to be associated with a poorer outcome, although confounding factors including comorbidities were not accounted for. Finally, Bechri et al.[29] reported ischemic stroke as an etiology associated with an increased risk of mortality. However, overall, limited conclusions could be drawn in relation to outcomes of SE in LMICs.

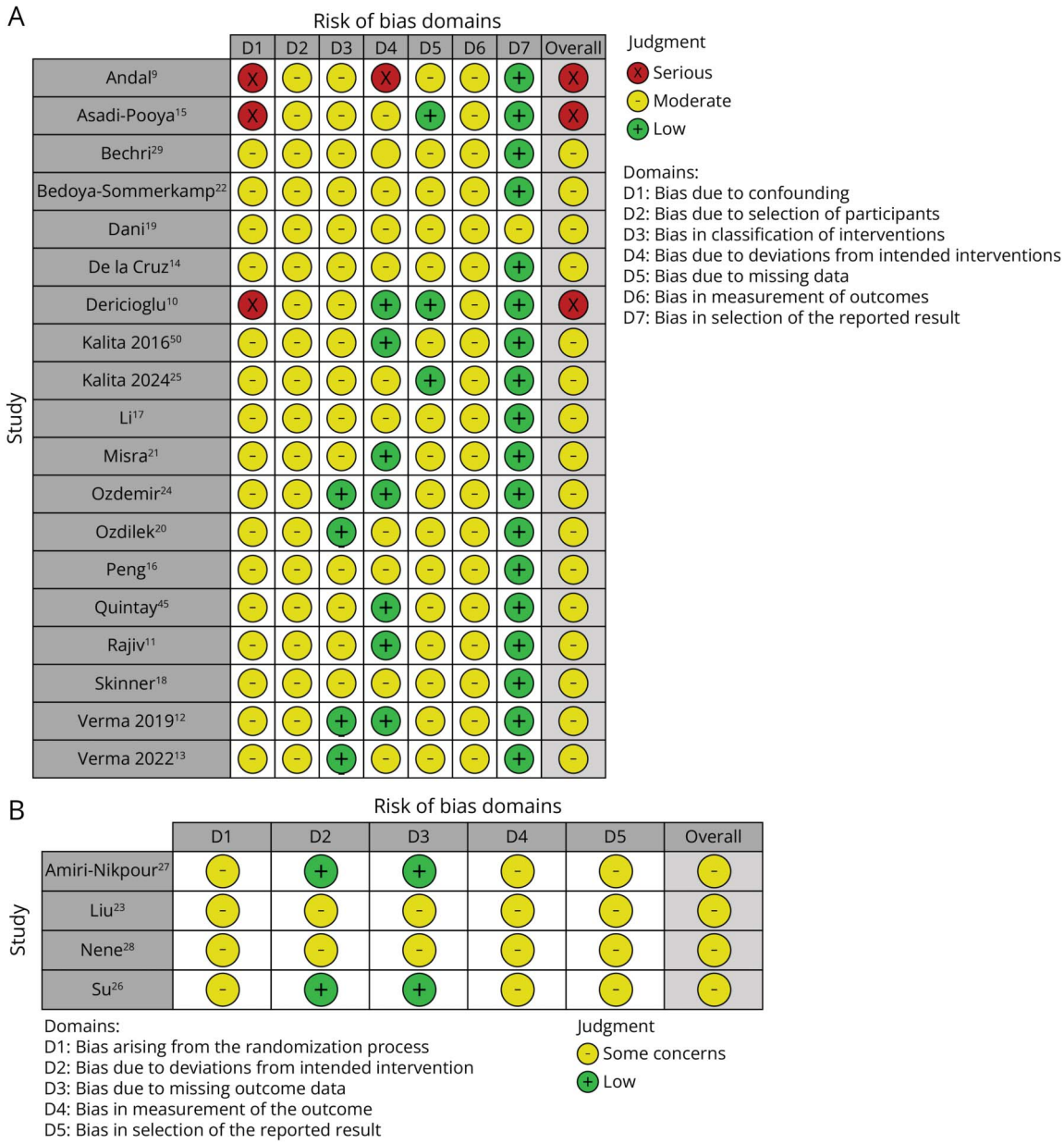
Discussion

The treatment of SE should be guided by protocols, but the global implementation of these clinical treatments has often been delayed and suboptimal.[30] A recent systematic review identified 16 international clinical practice guidelines published on the management of SE since 2010,[31] where authors concluded that the recommendations on general management were fragmented and organizational aspects were rarely considered in guidelines. Our systematic review of the management of SE in LMICs highlights the wide heterogeneity and nonstandardization in diagnosing and managing convulsive and nonconvulsive SE. In addition, there seems to be a great paucity of literature on SE from Africa, specifically Sub-Saharan Africa. Most studies in our review had limited or no access to cEEG, whether conducted in rural or urban areas. A lack of cEEG access likely affects the accurate diagnosis of NCSE in LMICs and presumably the lack of reporting in the literature. Individual management practices across centers were dictated by the limited access to BZDs and ASMs rather than established guidelines, highlighting the availability of drugs as a core barrier to the management of SE in LMICs.

In a global audit from 50 countries, SE etiologies differed remarkably among continents.[23] Infectious etiologies were most reported in Asian countries, with acute encephalitis occurring significantly more frequently than in other regions of the world. Among the included studies in this review, an AS etiology, which included infectious etiologies, was also noted to be the most common. This was followed by noncompliance to ASMs in patients with epilepsy.

An SE infectious etiology was as high as 67% in a Senegal study.[33] In India, this has been further documented to include neurocysticercosis (NCC),[5] with NCC increasing in prevalence both for epilepsy and SE in the region.[12] Because the remission of CSE depends on the timely identification and management of its etiology,[22] an infectious etiology is an important consideration in LMICs to guide appropriate and timely investigations from the onset. Although encephalitis

Figure 2 Schematic Representation of Risk-of-Bias Assessment: ROBINS-I (Panel A) and RoB-2 (Panel B)



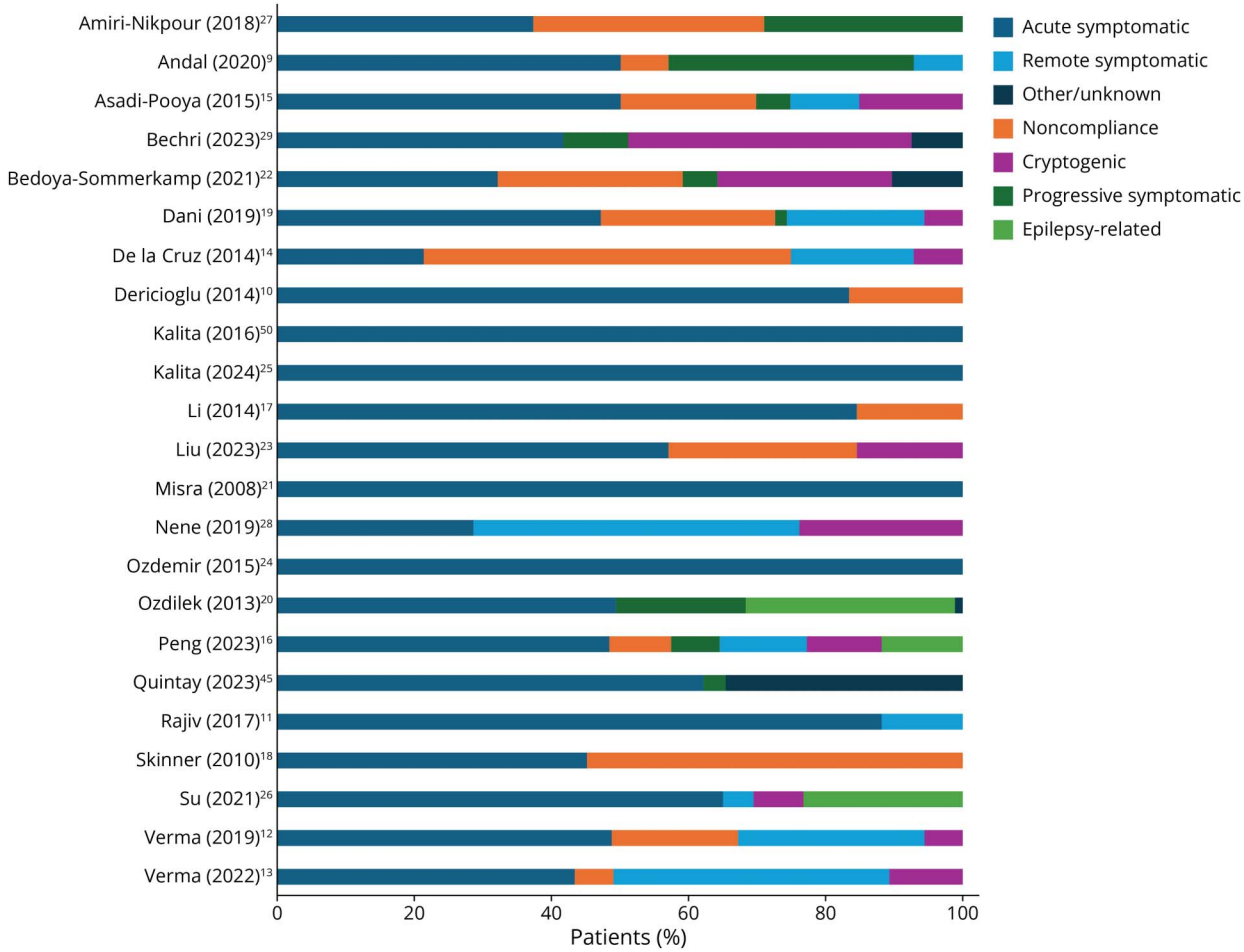
RoB-2 = Risk of Bias in Randomized Trials; ROBINS-I = Risk of Bias in Non-randomized Studies of Interventions.

was previously believed to be highly epileptogenic and a predictor of poorer outcomes,[34] this has more recently been documented not to affect mortality.[32,35] Proposed reasons could include younger ages and fewer comorbidities of patients presenting in LMICs with infectious etiologies.

Noncompliance to ASMs highlights another common barrier seen in epilepsy treatment in LMICs. Lack of education and culturally based stigma associated with epilepsy, as well as poor access to health care and limited access to affordable treatment, are contributing factors to this etiology,[36] which impair epilepsy treatment overall and confer a heightened tendency to develop SE.

Although EEG monitoring and the progression of EEG patterns are often used to guide CSE management and NCSE diagnosis, EEG monitoring was not mentioned in all studies. Typical clinical characteristics of NCSE may be extremely subtle and difficult to distinguish from another abnormal behavior, particularly outside intensive care unit settings.[9] While cEEG is routinely advocated for in HICs,[37] we found LMICs are limited in most of the cases to the availability of routine EEGs of 30–60 minutes. While cEEGs could potentially identify 80%–95% of NCSE cases, routine EEG could only document 45%–58% of patients with NCSE.[9] Among the studies included in our review, a lack of both machines and personnel to conduct tests and interpret results were some of

Figure 3 Etiologies of Status Epilepticus



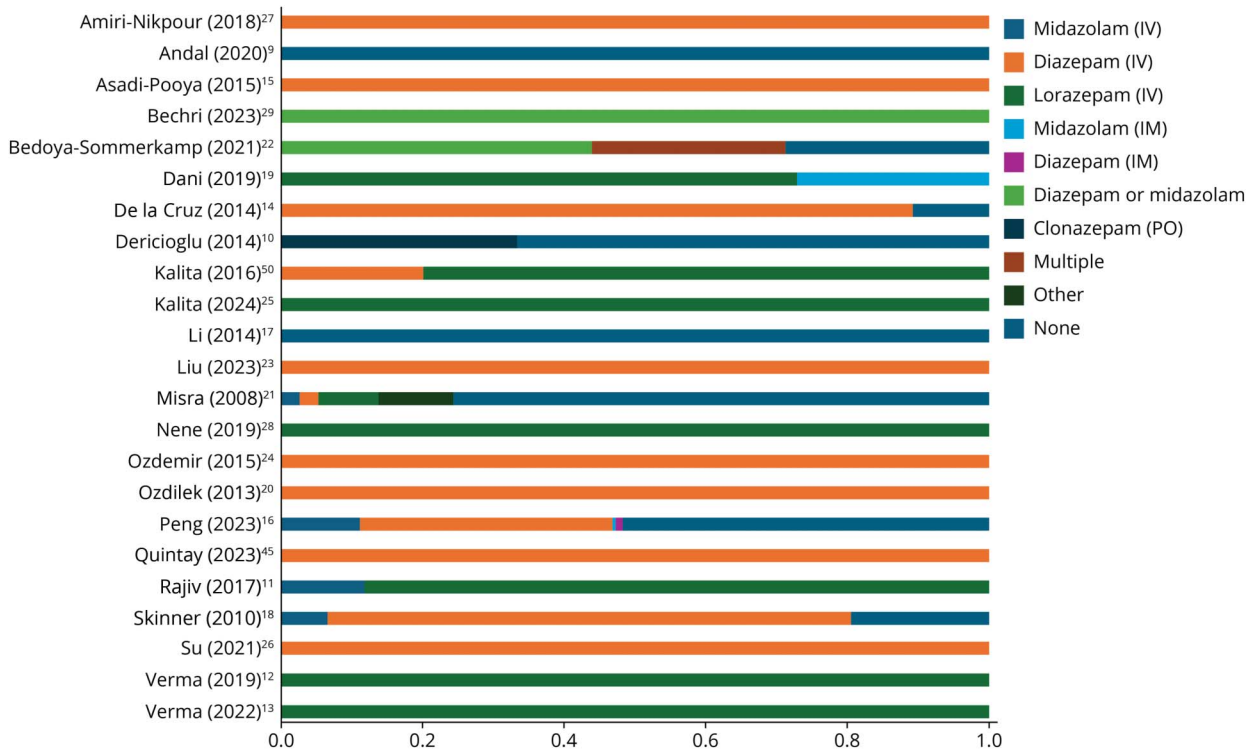
the cited reasons that led to the inability to use cEEG for patients with CSE or NCSE. In the absence of cEEG, studies across all continents used clinical assessments coupled with periodic routine EEG recordings to diagnose and manage SE.

The duration of CSE is an important indicator of whether a patient will respond to a first-line BZD,[38] with relationships demonstrated between treatment latency and BZD resistance. We did not have sufficient data to confirm this in our review. Obtaining an accurate estimate of CSE latency is often difficult in LMICs because of resource and health care limitations. This was demonstrated by the lack of reporting time to treatment or abort seizures in most of the included studies. In the studies that did, all durations reported were longer than 60 minutes, except for 2 studies.[15,16] In CSE episodes exceeding 60 minutes, the resistance to first-line BZDs is as high as 89%.[38] One study included in this review demonstrated that initial treatment with BZDs only controlled 30.3% of seizures,[16] similar to results from the SENSE registry.[39] In the included study,[16] the non-BZD group that was initially treated with ASMs or anesthesia showed a higher success rate, with no associated increased mortality or poor outcomes.[16] Despite recent evidence supporting the earlier use of anesthesia,[40] the timing and validation of this intervention have not been confirmed.

Up to 70% of patients with SE are underdosed with a first-line BZD,[41] although the risk of respiratory depression and hypotension with aggressive BZD use is less than that from ongoing CSE.[42] This finding was also congruent in our review, with only 1 BZD used most commonly and doses often not repeated. The choice of BZDs in studies varied greatly. There is level A evidence that in adults with CSE without established IV access, IM midazolam is more effective than IV lorazepam, with no significant difference in effectiveness demonstrated between lorazepam and diazepam.[43] In all the included studies, BZD availability dictated its use and recommendations of repeating doses and using a second BZD were not consistently followed.

The heterogeneity in choice and dose of ASMs used as second-line treatment among the studies was remarkable. The use of ASMs across all studies was dictated by availability. Although the Established Status Epilepticus Treatment Trial (ESETT) concluded similar efficacy and adverse event profiles with LEV, fosphenytoin, and VPA, only 2 studies in this

Figure 4 Summary of Benzodiazepine Use as First-Line Treatment



review prescribed fosphenytoin.[44] Similar to the conclusions of ESETT, one of the studies found no significant difference in the efficacy of LEV and VPA in an older population with CSE.[28] One study[45] that assessed the costs associated with SE noted that when comparing the costs of oral vs IV LEV and VPA, IV solutions cost more than 300×, leading to a much larger cumulative cost.

The most common ASMs in LMICs were VPA, LEV, PHT, and PB. PB has excellent seizure-terminating properties and is readily available in LMICs. Over its century of use, PB has demonstrated general tolerability and several clinical advantages, including rapid and long-lasting action and a favorable safety profile even at high doses.[46] Despite this, it is seldom used in adults in HICs. A recent review highlighted it as a highly cost-effective treatment for early and established SE and encouraged further trials focusing on its use.[46] There are remarkably few RCTs assessing PB as a treatment for SE in adults. However, 2 RCTs included in our review compared the efficacy of PB as a second-line ASM. The first affirmed comparable short and long-term effects for patients treated with PB vs VPA after SE[23] while the second showed that diazepam followed by PB had a higher CSE termination rate.[26] Both studies concluded that it is a reasonable choice of treatment in LMICs, and in China, it is still reportedly widely used because of its economic, effective, and familiar use.[28]

TPM is not mentioned in any of the recent clinical guidelines for SE, yet we found it to be used in several of the included studies. It is a broad-spectrum ASM with peak serum concentration 1–4 hours after enteral administration, and at times, more readily available than other IV ASMs in LMICs.[15] Its use in SE treatment has been confined to case series and cohort studies where it is used as a late treatment option; thus, its standalone efficacy cannot be confirmed. However, it seems to remain an option to treat SE when other protocols have failed or are unavailable.[15,47]

Mortality in patients with CSE from HICs has been reported to be 7.6%–22%.[48] The same review reported mortality in LMICs to be 16%–19.8%, which is still lower than the range found in our review. Unfortunately, owing to the wide differences in management practices among studies, we could not make associations between management and outcomes.

There are substantial limitations to this systematic review. The studies that met our inclusion criteria represented only a small number of regions, mostly in Asia, with fewer studies from the Middle East, Latin America, and North Africa. Other major regions, such as Sub-Saharan Africa, were entirely unrepresented. The lack of studies from these regions may be associated with resource limitations of health care systems to manage SE in patients or conduct epidemiologic studies of management and mortality in SE. In addition, some of the studies focused on specific patient populations, restricting our ability to generalize the findings from this review to unrepresented regions among LMICs.

More studies conducted in LMIC regions are needed. As with studies in HICs, studies in LMICs should be performed in

conformity with current guidelines for epidemiologic studies.[49] Representative population samples and incident cohorts should be studied, and clear etiologies, diagnostic information, management strategies including specific drugs with doses used, and outcomes should be documented. Standardized data collection will enable us to better identify the pitfalls and shortcomings of the management of SE in LMICs and consequently address them appropriately.

The large heterogeneity of treatment we observed illustrates the high degree of nonuniformity and lack of standardization in the identification and management of SE in LMICs. Many studies captured SE data on their cohort of patients by retrospective review of clinical records, which lends itself to limited control over selection and recall biases, as well as missing data.

Some strengths of this study are the comprehensive search strategy used and the inclusion of non-English studies to be as representative as possible of all LMICs.

SE in LMICs is diagnosed and managed in a widely heterogeneous manner, often led by local practices and drug availability, as opposed to established guidelines. Studies originating from Africa and Latin America remain very limited.

An infectious etiology is the commonest among LMICs. Similar to treatment in HICs, BZDs are underdosed. The choice of second-line ASMs is more likely to include older drugs, such as VPA, PHT, and PB, and oral ASMs are not uncommonly used. The lack of access to continuous EEG monitoring is a uniform barrier in many LMICs and a likely reason for the lack of literature in this regard. Poor health infrastructure and connectivity, delayed times in presenting to health care personnel in and out of hospital, lower ratios of doctors and specialists to the patient population, and increased medication prices all limit access to optimum SE care in these countries.

The nonuniformity of diagnostic and management practices in SE has highlighted the need for clinically appropriate guidelines in LMICs. These might include the incorporation of our findings from this review, including the use of different ASMs as first-line choices and recommendations on the best use of sequential routine EEGs in the absence of cEEG.

Acknowledgment

A.J. Soni acknowledges the International Federation of Clinical Neurophysiology who awarded her with an Education Award during her clinical epilepsy fellowship, during which she conducted this study.

Author Contributions

A.J. Soni: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. R.G. Couper: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. M.P. Vicuna: drafting/revision of the manuscript for content, including medical writing for content. J.G. Burneo: drafting/revision of the manuscript for content, including medical writing for content; study concept or design.

Study Funding

No targeted funding reported.

Disclosure

A.J. Soni, R.G. Couper, and M.P. Vicuna report no disclosures relevant to the manuscript. J.G. Burneo holds the Jack Cowin Endowed Chair in Epilepsy Research at Western University. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* December 9, 2024. Accepted in final form January 21, 2025. Submitted and externally peer reviewed. The handling editor was Editor-in-Chief José Merino, MD, MPhil, FAAN.

References

1. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus: report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*. 2015;56(10):1515-1523. doi:10.1111/epi.13121
2. Newton CR, Garcia HH. Epilepsy in poor regions of the world. *Lancet*. 2012;380(9848):1193-1201. doi:10.1016/S0140-6736(12)61381-6
3. Lee B; Asian Status Epilepticus Survey Group. Treatment gap for convulsive status epilepticus in resource-poor countries. *Epilepsia*. 2018;59(suppl 2):135-139. doi:10.1111/epi.14484
4. Levira F, Thurman DJ, Sander JW, et al. Premature mortality of epilepsy in low- and middle-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia*. 2017;58(1):6-16. doi:10.1111/epi.13603
5. Murthy JM, Jayalaxmi SS, Kanikannan MA. Convulsive status epilepticus: clinical profile in a developing country. *Epilepsia*. 2007;48(12):2217-2223. doi:10.1111/j.1528-1167.2007.01214.x
6. Marshall C, Olaniyan T, Jalloh AA, et al. Survey of the perceived treatment gap in status epilepticus care across Sub-Saharan countries from the perspective of healthcare providers. *Epilepsy Behav*. 2021;125:108408. doi:10.1016/j.yebeh.2021.108408
7. Kwon CS, Wagner RG, Carpio A, Jette N, Newton CR, Thurman DJ. The worldwide epilepsy treatment gap: a systematic review and recommendations for revised definitions: a report from the ILAE Epidemiology Commission. *Epilepsia*. 2022;63(3):551-564. doi:10.1111/epi.17112
8. Diop AG, Hesdorffer DC, Logroscino G, Hauser WA. Epilepsy and mortality in Africa: a review of the literature. *Epilepsia*. 2005;46(suppl 11):33-35. doi:10.1111/j.1528-1167.2005.00405.x
9. Andal VMD, Espiritu AI, Geronimo MAG, Salonga-Quimpo RAM, Gosiengfiao KTP, Fernandez MLL. Clinical features and outcomes of nonconvulsive status epilepticus in a developing country: a 5-year retrospective study. *Epilepsy Behav*. 2020;113:107547. doi:10.1016/j.yebeh.2020.107547
10. Dericioglu N, Arsava EM, Topcuoglu MA. The clinical features and prognosis of patients with nonconvulsive status epilepticus in the neurological intensive care unit of a tertiary referral center in Turkey. *Clin EEG Neurosci*. 2014;45(4):293-298. doi:10.1177/1550059413503639
11. Rajiv KR, Radhakrishnan A. Status epilepticus in pregnancy: etiology, management, and clinical outcomes. *Epilepsy Behav*. 2017;76:114-119. doi:10.1016/j.yebeh.2017.07.002
12. Verma A, Kiran K, Vaishya GP, Kumar A. Adult convulsive status epileptic us: clinical, etiological, and predictors of outcome study from rural population of North India. *Int J Neurosci*. 2019;129(6):573-579. doi:10.1080/00207454.2018.1552692
13. Verma A, Kumar A, Sachan D. Comparison of clinical profile and outcome of de novo convulsive status epilepticus with those with a past history of epilepsy in the elderly populace. *Acta Neurol Taiwan*. 2022;31(3)(3):131-136.
14. De la Cruz WF, Zapata WR, Delgado JC, Mija L. Estado epiléptico convulsivo en adultos atendidos en el Instituto Nacional de Ciencias Neurológicas de Lima, Perú 2011-2013. *Rev Neuropsiquiatr*. 2014;77(4):236-241. doi:10.20453/rnp.2014.2193
15. Asadi-Pooya AA, Jahromi MJ, Izadi S, Emami Y. Treatment of refractory generalized convulsive status epilepticus with enteral topiramate in resource limited settings. *Seizure*. 2015;24:114-117. doi:10.1016/j.seizure.2014.09.009
16. Peng W, Lu L, Wang P, et al. The initial treatment in convulsive status epilepticus in China: a multi-center observational study. *Epilepsy Res*. 2023;197:107245. doi:10.1016/j.eplepsyres.2023.107245

17. Li Y, Tian L, Zeng T, Chen J, Chen L, Zhou D. Clinical features and outcome of super-refractory status epilepticus: a retrospective analysis in West China. *Seizure*. 2014; 23(9):722-727. doi:10.1016/j.seizure.2014.05.014
18. Skinner HJ, Dubon-Murcia SA, Thompson AR, et al. Adult convulsive status epilepticus in the developing country of Honduras. *Seizure*. 2010;19(6):363-367. doi: 10.1016/j.seizure.2010.05.007
19. Dani R, Sodani A, Telang K, Nigam R. Determinants of outcome in convulsive status epilepticus in adults: an ambispective study from Central India. *Ann Indian Acad Neurol*. 2019;22(1):84-90. doi:10.4103/aian.AIAN_466_17
20. Ozdilek B, Midi I, Agan K, Bingol CA. Episodes of status epilepticus in young adults: etiologic factors, subtypes, and outcomes. *Epilepsy Behav*. 2013;27(2):351-354. doi: 10.1016/j.yebeh.2013.02.023
21. Misra UK, Kalita J, Nair PP. Status epilepticus in central nervous system infections: an experience from a developing country. *Am J Med*. 2008;121(7):618-623. doi:10.1016/j.amjmed.2008.02.012
22. Bedoya-Sommerkamp M, Chau-Rodriguez VH, Medina-Ranilla J, et al. Convulsive status epilepticus in a cohort of patients from a Peruvian academic hospital. *J Epilepsy Res*. 2021;11(1):83-92. doi:10.14581/jer.21011
23. Liu G, Wang Y, Tian F, et al. Long-term follow-up of phenobarbital versus valproate for generalized convulsive status epilepticus in adults: a randomized clinical trial. *Epilepsy Res*. 2023;195:107187. doi:10.1016/j.eplepsyres.2023.107187
24. Ozdemir HH, Mungen B, Ilhan S. Evaluation of the efficacy of sodium valproate in convulsive status epilepticus following to ischemic stroke. *Arq Neuropsiquiatr*. 2015; 73(4):293-297. doi:10.1590/0004-282X20150001
25. Kalita J, Nizami FM, Kumar R. Status epilepticus in tuberculous meningitis. *Epilepsy Behav*. 2024;159:109986. doi:10.1016/j.yebeh.2024.109986
26. Su Y, Huang H, Jiang M, et al. Phenobarbital versus valproate for generalized convulsive status epilepticus in adults (2): a multicenter prospective randomized controlled trial in China (China 2-P vs. V). *Epilepsy Res*. 2021;177:106755. doi:10.1016/j.eplepsyres.2021.106755
27. Amiri-Nikpour MR, Nazarbaghi S, Eftekhari P, et al. Sodium valproate compared to phenytoin in treatment of status epilepticus. *Brain Behav*. 2018;8(5):e00951. doi: 10.1002/brb3.951
28. Nene D, Mundlamuri RC, Satishchandra P, et al. Comparing the efficacy of sodium valproate and levetiracetam following initial lorazepam in elderly patients with generalized convulsive status epilepticus (GCSE): a prospective randomized controlled pilot study. *Seizure*. 2019;65:111-117. doi:10.1016/j.seizure.2019.01.015
29. Bechri I, Shimi A, Derkaoui A, Khatouf M. Status epilepticus in a tertiary care hospital in Morocco: a retrospective analysis. *Cureus*. 2023;15(12):e50591. doi:10.7759/cureus.50591
30. Neligan A, Noyce AJ, Gosavi TD, Shorvon SD, Kohler S, Walker MC. Change in mortality of generalized convulsive status epilepticus in high-income countries over time: a systematic review and meta-analysis. *JAMA Neurol*. 2019;76(8):897-905. doi: 10.1001/jamaneurol.2019.1268
31. Vignatelli L, Tontini V, Meletti S, et al. Clinical practice guidelines on the management of status epilepticus in adults: a systematic review. *Epilepsia*. 2024;65(6): 1512-1530. doi:10.1111/epi.17982
32. Ferlisi M, Hocker S, Trinka E, Shorvon S; International Steering Committee of the StEp Audit. Etiologies and characteristics of refractory status epilepticus cases in different areas of the world: results from a global audit. *Epilepsia*. 2018;59(suppl 2): 100-107. doi:10.1111/epi.14496
33. Diop-Sene MS, Seck LB, Toure K, et al. Management of neurological emergencies in developing country: example of Senegal [in French]. *Revue Neurol (Paris)*. 2012; 168(3):216-220. doi:10.1016/j.neurol.2011.12.005
34. Holtkamp M. The anaesthetic and intensive care of status epilepticus. *Curr Opin Neurol*. 2007;20(2):188-193. doi:10.1097/WCO.0b013e328042bacb
35. Jayalakshmi S, Ruikar D, Vooturi S, et al. Determinants and predictors of outcome in super refractory status epilepticus--a developing country perspective. *Epilepsy Res*. 2014;108(9):1609-1617. doi:10.1016/j.eplepsyres.2014.08.010
36. Soni A, Pan EL, Tucker L. Anterior temporal lobectomy: a cross-sectional observational study of potential surgical candidates at a single institute. *Surg Neurol Int*. 2021; 12:565. doi:10.25259/SNI_796_2021
37. Laccheo I, Sonmezturk H, Bhatt AB, et al. Non-convulsive status epilepticus and non-convulsive seizures in neurological ICU patients. *Neurocrit Care*. 2015;22(2):202-211. doi:10.1007/s12028-014-0070-0
38. Burman RJ, Rosch RE, Wilmshurst JM, et al. Why won't it stop? The dynamics of benzodiazepine resistance in status epilepticus. *Nat Rev Neurol*. 2022;18(7):428-441. doi:10.1038/s41582-022-00664-3
39. Kellinghaus C, Rossetti AO, Trinka E, et al. SENSE registry for status epilepticus. *Epilepsia*. 2018;59(suppl 2):150-154. doi:10.1111/epi.14495
40. De Stefano P, Baumann SM, Semmlack S, et al. Safety and efficacy of coma induction following first-line treatment in status epilepticus: a 2-center study. *Neurology*. 2021; 97(6):e564-e576. doi:10.1212/WNL.0000000000012292
41. Brigo F, Bragazzi NL, Bacigaluppi S, Nardone R, Trinka E. Is intravenous lorazepam really more effective and safe than intravenous diazepam as first-line treatment for convulsive status epilepticus? A systematic review with meta-analysis of randomized controlled trials. *Epilepsy Behav*. 2016;64(Pt A):29-36. doi:10.1016/j.yebeh.2016.09.020
42. Guterman EL, Sanford JK, Betjemann JP, et al. Prehospital midazolam use and outcomes among patients with out-of-hospital status epilepticus. *Neurology*. 2020; 95(24):e3203-e3212. doi:10.1212/WNL.0000000000010913
43. Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr*. 2016;16(1):48-61. doi:10.5698/1535-7597-16.1.48
44. Chamberlain JM, Kapur J, Shinnar S, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. *Lancet*. 2020;395(10231): 1217-1224. doi:10.1016/S0140-6736(20)30611-5
45. Quintay P, Quiles LEP, Roxas AA Jr. Anticonvulsant drug regimen and cost of acute treatment for status epilepticus in a Philippine tertiary hospital: a retrospective cohort study. *Acta Med Philipp*. 2023;57(6):24-29. doi:10.47895/amp.vi0.4921
46. Trinka E. Phenobarbital in Status epilepticus: rediscovery of an effective drug. *Epilepsy Behav*. 2023;141:109104. doi:10.1016/j.yebeh.2023.109104
47. Fechner A, Hubert K, Jahnke K, et al. Treatment of refractory and superrefractory status epilepticus with topiramate: a cohort study of 106 patients and a review of the literature. *Epilepsia*. 2019;60(12):2448-2458. doi:10.1111/epi.16382
48. Logroscino G. Status epilepticus: different venues, different resources, but similar prognosis. *Eur J Neurol*. 2009;16(4):436-437. doi:10.1111/j.1468-1331.2008.02402.x
49. Thurman DJ, Beghi E, Begley CE, et al. Standards for epidemiologic studies and surveillance of epilepsy. *Epilepsia*. 2011;52(suppl 7):2-26. doi:10.1111/j.1528-1167.2011.03121.x
50. Kalita J, Mani VE, Bhoi SK, Misra UK. Status epilepticus in scrub typhus. *Epilepsia*. 2016;57(7):e125-e128. doi:10.1111/epi.13412