Etiologies and characteristics of refractory status epilepticus cases in different areas of the world: Results from a global audit

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Summary

To describe the demographics, etiologies, types of status epilepticus (SE), and outcomes in people with refractory and super-refractory SE from around the world, we prospectively collected cases of refractory SE (RSE) treated with continuous intravenous anesthetic drugs in an intensive care unit setting through online questionnaires using “active surveillance.” We collected information about 776 cases of RSE in 50 countries over 4 years. Control of SE was achieved in 74% of the cases. Neurologic outcomes were poor in 41% of patients, and 24% died. Good outcome was associated with younger age and a history of epilepsy. Etiology strongly influenced the outcome. Patients from Asia were younger, more frequently presented with convulsive SE, and were more frequently affected by infectious etiologies when compared with patients from Europe and the Americas. Despite these differences, outcomes were similar in all countries. Demographics of patients with RSE in a global audit are similar to those in prior single center series, providing evidence of generalizability of those studies. Important differences exist among patients with RSE from different regions of the world, but these do not seem to significantly influence patient outcomes.

Key Points

- We collected information about 776 cases of RSE treated with continuous IV anesthetic drugs in 50 countries around the world
- Good outcome was associated with younger age and a history of epilepsy; etiology strongly influenced the outcome
- Patients from Asia were younger, more frequently presented with convulsive SE, and were more frequently affected by infectious etiologies
- Important differences exist among patients with RSE from different regions of the world, but these do not seem to influence patient outcomes

1 INTRODUCTION

Refractory status epilepticus (RSE) is a dangerous condition, with a mortality rate of 24%-38% in recent series,[1], [2] higher in prolonged episodes.[3]A generally accepted definition of RSE is a seizure that persists after two antiseizure drugs, typically including a benzodiazepine. At this stage, most protocols suggest treatment with continuous intravenous anesthetic drugs to promptly stop seizure activity and

prevent long-term neuronal damage, further refractoriness,[4], [5] and severe acute systemic consequences, especially in convulsive status epilepticus (SE). The current evidence guiding optimal management of RSE is mostly based on small series, given the rarity of the condition.[6] For these reasons, there has been an increasing interest in multinational registries.[7], [8]

The underlying etiology of SE is considered the most important prognostic factor determining outcome.[9] Apart from the treatment, etiology itself significantly differs in developing countries as compared to the Western world, with acute symptomatic etiologies being more frequent in developing countries.[10], [11] In this study, we prospectively collected information about cases of RSE treated with continuous intravenous (IV) anesthetic drugs in different regions of the world.

2 MATERIALS AND METHODS

Details about the audit procedures have been published previously.[12] Briefly, this was an anonymized online registry, collecting information prospectively from neurologists and intensivists caring for patients with RSE not responding to first-line therapy, admitted to an intensive care unit (ICU), and treated with continuous IV anesthetic drugs, through online questionnaires. The “active surveillance” method, which utilized monthly reminders sent to all participating physicians, ensured maximal reporting. A modified Rankin Scale of 0-3 was considered a good outcome.[13]

All data were analyzed using statistical software (SPSS Statistics, version 20; IBM, Armonk, NY, USA). When comparing continuous variables, Student *t* test and Mann-Whitney test were used. The analysis of categorical variables was performed using chi-square and Fisher’s exact tests and analysis between groups with analysis of variance and Kruskal-Wallis.

3 RESULTS

The data collection started on March 1, 2013 and was terminated after 4 years. In total, 776 cases were collected from 166 different physicians (see list of all contributors in Appendix Appendix 1). A map of the 50 countries involved is shown in Figure 1, and the number of cases contributed per country in Figure 2. Patients were from Europe (n = 408, 56%), Asia (n = 169, 23%), the Americas (n = 131, 18%), Australia and New Zealand (n = 17, 2%), and Africa (n = 9, 1%). The clinical characteristics of patients are summarized in Table 1. The majority of patients (n = 474, 63%) had no history of epilepsy, and the most common single etiology was cryptogenic (n = 200, 26.1%). Among those with cryptogenic RSE, 78 (39%) had a

positive history of epilepsy, 119 (59.5%) had new onset RSE, and in three patients (2%) history of epilepsy was uncertain.

Figure 1
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Map of involved countries

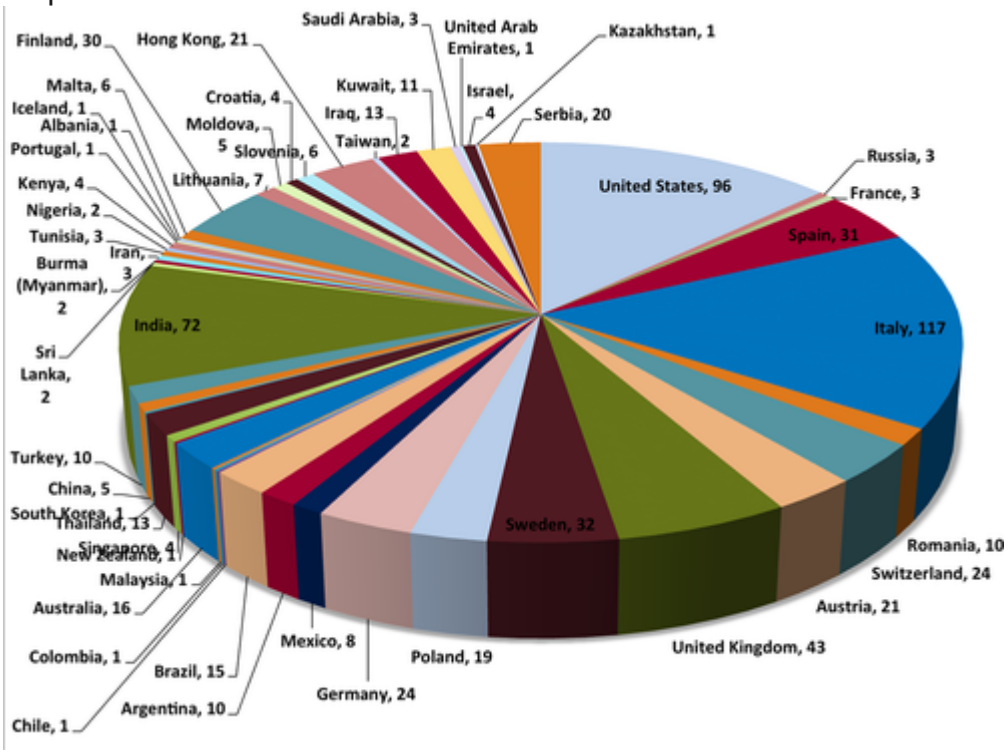

Figure 2
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Origin of patients

Table 1. Clinical characteristics of the 776 patients[a]

	n	%
Age	39.8 ± 25.9 years (mean ± SD), 0-92 years (range)	
Gender		
Male	423	55
Female	353	45
History of epilepsy		
Yes	288	38
No	474	63
Etiologies, can be multiple per patient		
Unknown/cryptogenic	200	26.1
Infections, all	148	19.6
Acute encephalitis	81	10.6
Acute meningitis	19	2.5
Other infections	50	6.5
Vascular, including stroke	111	14.5
Anoxic, including cardiac arrest	85	11.1
Antiseizure drug reduction/withdrawal	56	7.3
Cerebral tumor	47	6.1
Miscellaneous[b]	43	5.6
Trauma	42	5.5
Metabolic	36	4.7
Alcohol	35	4.6
Immunological, all	24	3.1

	n	%
NMDAR Ab	8	1.0
VGKA Ab	2	0.3
Lupus, seropositive	3	0.4
Other	11	1.4
Genetic/chromosomal	18	2.3
Other toxins	12	1.6
Mitochondrial disease	11	1.4

- Ab, antibody; NMDAR, *N*-methyl-D-aspartate receptor.
- a Percentages were calculated from available data with denominators provided.
- b Includes eclampsia, posterior reversible encephalopathy syndrome, cortical dysplasia, and not classified.

SE was convulsive in 55% of cases, nonconvulsive in 19%, convulsive evolving to nonconvulsive in 21%, and of other semiology (epilepsia partialis continua, absence status, other) in 4%. Mean duration of ICU stay was 18.41 ± 22.8 days.

3.1 Regional differences

There were too few patients from Africa and Oceania to justify subgroup analyses. Patients from Asia were significantly younger than those from Europe and the Americas (mean age = 22.4, 48.2, and 40.5 years, $P < .001$) and more frequently presented with convulsive SE compared with nonconvulsive forms (71%, 53%, and 44%, $P < .001$). The ICU duration was longer in Asia (mean = 22.8 ± 24.1 days) than in Europe (16.3 ± 18.9 days, $P < .05$) or in the Americas (19.31 ± 26.3 days).

There were some notable differences regarding etiologies of SE (Table 2). In Asia, the most frequently reported etiology was infectious (n = 59, 30.1%), whereas infectious etiology represented only 15.4% (n = 23) of cases in the Americas and 12.3% (n = 56) of cases in Europe. In particular, the percentage of cases with acute encephalitis was significantly higher in Asia (n = 41, 20.9%) than in Europe (n = 26, 5.7%) or the Americas (n = 7, 4.7%, $P < .01$). Vascular etiologies were more frequent in Europe (n = 75, 16.6%) than in Asia (n = 11, 5.6%, $P < .01$). There was a

nonsignificant trend toward a higher incidence of traumatic etiologies in Europe (n = 28, 6.2%) and the Americas (n = 7, 4.7%) than in Asia (n = 1, 0.5%).

Table 2. Etiologies among continents[a]

	Asia, n (%)	Europe, n (%)	Americas, n (%)
Unknown/cryptogenic	50 (25.5)	98 (21.6)	34 (22.8)
Vascular, including stroke	11 (5.6)	75 (16.6)	17 (11.4)
Anoxic, including cardiac arrest	13 (6.6)	51 (11.3)	17 (11.4)
Trauma	1 (0.5)	28 (6.2)	7 (4.7)
Infection, all	59 (30.1)	56 (12.3)	23 (15.4)
Acute encephalitis	41 (20.9)	26 (5.7)	7 (4.7)
Acute meningitis	6 (3.1)	9 (2.0)	3 (2.0)
Other infection	12 (6.1)	21 (4.6)	13 (8.7)
Alcohol	0 (0)	28 (6.2)	6 (4.0)
Other toxins	4 (2.0)	3 (0.7)	3 (2.0)
Metabolic	11 (5.6)	17 (3.8)	7 (4.7)

	Asia, n (%)	Europe, n (%)	Americas, n (%)
Cerebral tumor	5 (2.6)	33 (7.3)	6 (4.0)
Antiseizure drug reduction/withdrawal	16 (8.2)	20 (4.4)	14 (9.4)
Genetic/chromosomal	6 (3.1)	8 (1.8)	2 (1.3)
Immunological, all	7 (3.5)	9 (1.9)	6 (4.0)
Mitochondrial disease	4 (2.0)	4 (0.9)	3 (2.0)
Miscellaneous[b]	9 (4.6)	23 (5.1)	4 (2.7)

- a Percentages were calculated from available data with denominators provided.
- b Includes eclampsia, posterior reversible encephalopathy syndrome, cortical dysplasia, others, and not classified.

3.2 Outcomes

In 686 cases, information about the outcome was provided; 510 patients (74%) recovered, 148 patients (22%) died during treatment, and 28 patients (4%) had therapy actively withdrawn.

The neurological status of the patients at the end of anesthesia was good in 35% of patients and poor in 41%, and 24% of patients died. Outcomes in patients with long-term outcome data provided (n = 208) are shown in Table 3. There was a higher proportion of patients with better outcome at 6-month follow-up.

Table 3. Neurological outcome of patients with long-term follow-up available[a]

Modified Rankin Scale	At end of anesthesia, n (%)	At 6-month follow-up, n (%)
0—No symptoms	18 (9)	31 (15)
1—No significant disability; able to carry out all usual activities, despite some symptoms	30 (15)	46 (22)
2—Slight disability; able to look after own affairs without assistance, but unable to carry out all previous activities	21 (10)	24 (12)
3—Moderate disability; requires some help, but able to walk unassisted	27 (13)	42 (20)
4—Moderately severe disability; unable to attend to own bodily needs without assistance, and unable to walk unassisted	51 (25)	23 (11)
5—Severe disability; requires constant nursing care and attention, bedridden, incontinent	54 (27)	29 (14)
6—Dead	n.a.	13 (6)
Total	201 (100)	208 (100)

- n.a., not applicable.
- a Percentages were calculated from the known cases.

No differences were found in outcome with respect to gender or type of SE. History of epilepsy and younger age were positively associated with recovery from SE ($P < 0.001$). As expected, etiology strongly influenced outcome (Table 4). Patients with postanoxic SE had the worst outcomes, as did those with metabolic etiologies or

acute encephalitis when compared with other etiologies. The patients with the best long-term outcomes were those where the etiology of the status was classified as due to “antiseizure drug withdrawal,” and the worst outcomes statistically were those classified as due to anoxia (Table 5).

Table 4. Association of etiology with outcome[a]

Etiology of status epilepticus	Recovered, n (%)	Not recovered, n (%)[b]
Antiseizure drug reduction/withdrawal	44 (94)	3 (6)
Genetic/chromosomal	17 (94)	1 (6)
Trauma	31 (84)	6 (16)
Mitochondrial disease	5 (83)	1 (17)
Immunological, all	20 (83)	4 (17)
Acute meningitis	14 (82)	3 (18)
Miscellaneous[c]	32 (82)	7 (18)
Other infection	34 (79)	9 (21)
Other toxins	7 (78)	2 (22)
Cerebral tumor	33 (75)	11 (25)

Etiology of status epilepticus	Recovered, n (%)	Not recovered, n (%)[b]
Unknown/cryptogenic	132 (75)	45 (25)
Alcohol	25 (74)	9 (26)
Vascular, including stroke	74 (73)	28 (27)
Acute encephalitis	45 (64)	25 (36)
Metabolic	20 (59)	14 (41)
Anoxic, including cardiac arrest	37 (52)	34 (48)

- a Percentages were calculated from available data with denominators provided.
- b Includes patients who died during treatment and patients who had therapy actively withdrawn and then died or had a severe disability.
- c Includes eclampsia, posterior reversible encephalopathy syndrome, cortical dysplasia, others, and not classified.

Table 5. Association of etiology with neurological outcome at 6 months[a]

Etiology of status epilepticus	Good, mRS 0-3, n (%)	Poor, mRS 4-5, n (%)	Dead, mRS 6, n (%)
Genetic/chromosomal	5 (63)	3 (38)	0 (0)
Antiepileptic drug reduction/withdrawal	23 (56)	15 (37)	3 (7)

Etiology of status epilepticus	Good, mRS 0-3, n (%)	Poor, mRS 4-5, n (%)	Dead, mRS 6, n (%)
Other toxins	4 (50)	3 (38)	1 (13)
Mitochondrial disease	3 (50)	2 (33)	1 (17)
Miscellaneous[b]	39 (49)	31 (39)	10 (13)
Cerebral tumor	15 (41)	16 (43)	6 (16)
Trauma	14 (40)	15 (43)	6 (17)
Other infection	14 (35)	17 (43)	9 (23)
Alcohol	10 (33)	11 (37)	9 (30)
Unknown/cryptogenic	46 (32)	67 (46)	32 (22)
Acute meningitis	5 (31)	8 (50)	3 (19)
Immunological, all	11 (31)	15 (42)	10 (28)
Metabolic	9 (30)	9 (30)	12 (40)
Acute encephalitis	18 (26)	30 (43)	22 (31)

Etiology of status epilepticus	Good, mRS 0-3, n (%)	Poor, mRS 4-5, n (%)	Dead, mRS 6, n (%)
Vascular, including stroke	23 (25)	44 (48)	24 (26)
Anoxic, including cardiac arrest	13 (19)	26 (38)	29 (43)

- mRS, modified Rankin Scale.
- a Percentages were calculated from available data with denominators provided.
- b Includes eclampsia, posterior reversible encephalopathy syndrome, cortical dysplasia, others, and not classified.

In the analysis between geographical regions, we did not find any significant differences in rate of success in controlling SE or in the neurological outcome of patients (Figures 3 and 4).

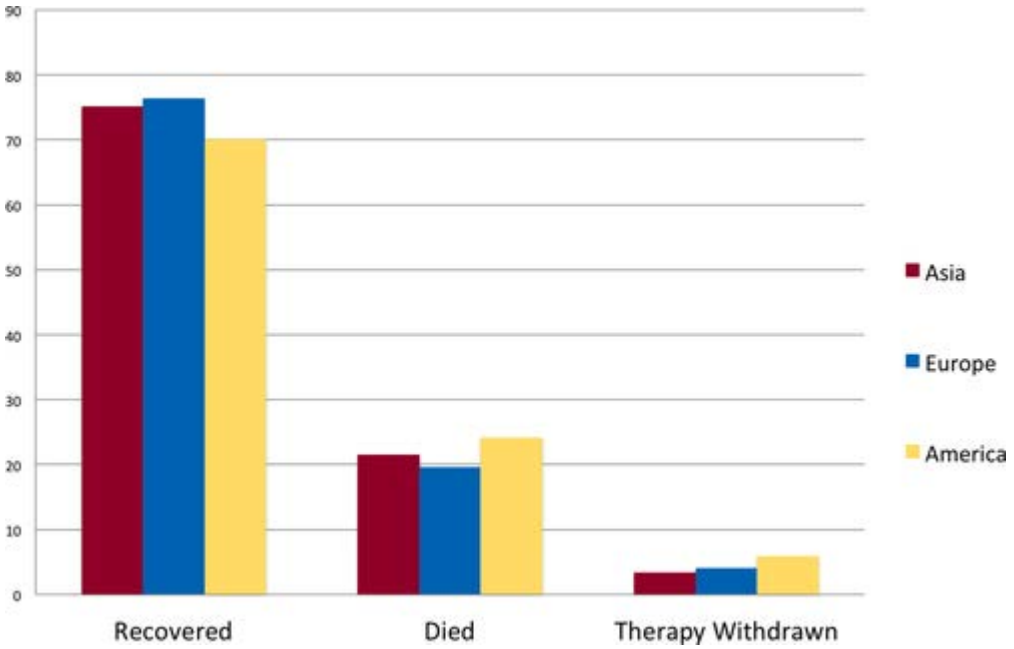

Figure 3
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Outcome of status epilepticus episodes

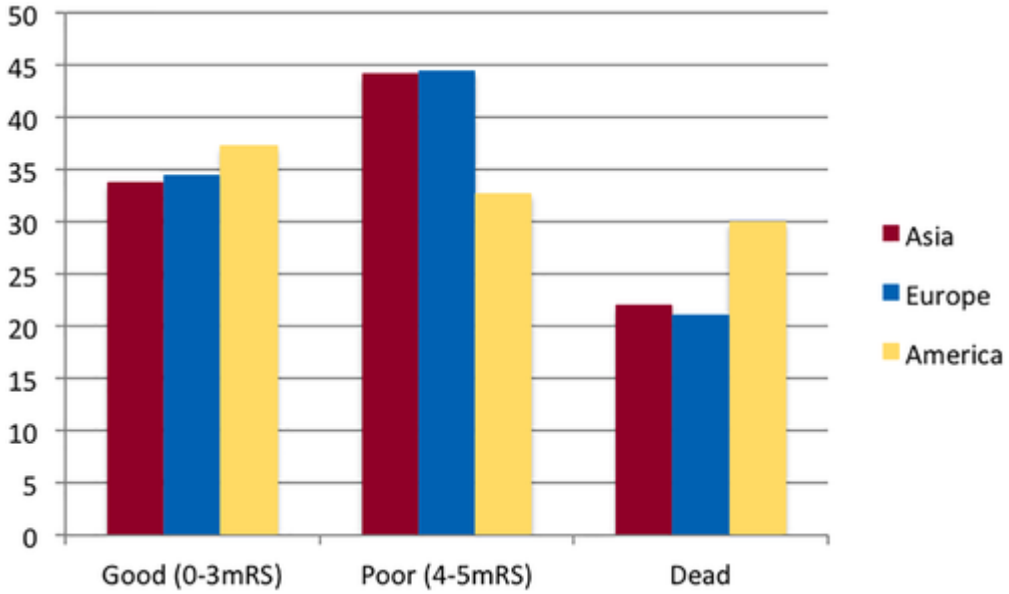

Figure 4

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Neurological outcome of patients at the end of anesthesia. mRS, modified Rankin Scale

4 DISCUSSION

In studies on RSE, the setting (ICU, academically driven, general hospital, rural hospital) and the geographical region may have an important impact on the results.[10], [14], [15]Observational studies are almost the only ones available in RSE, and the validity of such studies depends on the range of participation and the quality of their data. This is to our knowledge the largest and most widely collected series of RSE treated with continuous IV anesthetic drugs, although we acknowledge limitations in drawing conclusions about associations, given the nonsystematic method of collection. Our case definition requires the administration of IV anesthetic drugs, and not all definitions of RSE have this stipulation. We introduced this stipulation to avoid confusion among the participants and to ensure that all the participants in the audit are severe cases (albeit in the recognition that SE stops in some milder cases without continuous IV anesthetic drugs, and there are also cases that would be treated with IV anesthetic drugs in some countries but not in others, especially in the poorest regions of the world).

To ensure accuracy and completeness of the data, we modified the format of the questionnaires several times, but as increasing complexity reduced the number of cases reported, we had to compromise on a limited dataset. We also did not make any complex statistical analysis of the data regarding the limitations of case selection bias.[16] Despite these limitations, this registry adds important information to our knowledge of the demographics, types, and etiologies of RSE treated with continuous IV anesthetic drugs around the world.

As expected, etiology of SE and characteristics of patients can significantly differ in Asian countries as compared to the Western world.[10], [14] In this study, patients from Asia were younger; this could simply reflect the lower mean age of the Asian population. We found less prevalence of nonconvulsive status in Asian countries, presumably because of lower availability of continuous electroencephalographic monitoring. Globally, cryptogenic SE was the most frequent cause of RSE around the world. As most of these cases had no history of epilepsy, future research must focus on identifying causes of cryptogenic RSE and in particular on autoimmune etiologies, which probably account for a significant number of these cases. As expected, anoxic SE has the worst outcome; acute encephalitis and metabolic etiologies are also associated with poor outcomes.

Etiologies differ remarkably among continents. In Asian countries, infectious etiologies were the most commonly reported, with acute encephalitis occurring significantly more frequently than in other regions of the world. Acute encephalitis has been associated with refractoriness to treatment and higher mortalities in prior studies.[17]-[19] A fascinating finding of this audit is that, despite such great differences in patients' and SE characteristics, outcomes around the world were largely similar. It is possible that such great differences in etiologies and SE characteristics are somehow compensated by other factors, like younger age, and the nature of this study does not allow for a full exploration of these relationships.

Data from this audit have been reviewed with all the participant doctors at the 6th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures, where further analyses have been planned and future research discussed.

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DISCLOSURE

The authors have no conflicts of interest to report. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix 1: List of all contributing doctors

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