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Inpatient treatment costs of status epilepticus in adults in Germany

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ABSTRACT

Purpose: Status epilepticus (SE) is an important neurological emergency and a significant source of direct costs related to hospitalization; however, no cost-of-illness (COI) studies have been performed in Europe. The objective of this study was to determine and characterize hospital costs related to the acute inpatient treatment of SE and to provide national estimates of SE hospitalization costs.

Methods: Adult inpatient treatment costs related to SE and costs attributable to epilepsy-related hospital admissions were derived from billing data of participating hospitals.

Results: During the 4-month study period a total of 96 patients (59.5 ± 21.6 years; 52 male) received inpatient treatment for epilepsy-related reasons, 10 of these (10.4%) were treated for SE. Epilepsy was newly diagnosed in 30/96 patients (31.3%), of whom five presented with SE. The admission costs related to SE (€8347 ± 10,773 per patient per admission) were significantly higher than those related to admissions of patients with newly diagnosed (€1998 ± 1089; $p = 0.014$) or established epilepsy (€3475 ± 4413; $p = 0.026$). Of the total inpatient costs (€346,319) 24.4% were attributable to SE, 14.4% to newly diagnosed epilepsy without SE ($n = 25$) and 61.2% to complications of established epilepsy ($n = 61$). Extrapolation to the whole of Germany (population 82 million) indicates that SE causes hospital costs of more than €83 million per year while the total of epilepsy-related inpatient treatment costs amounts to €342 million.

Conclusion: Acute treatment of SE is responsible for a high proportion of hospital costs associated with epilepsy. With a high incidence of SE in the elderly population, the health care systems will face an increasing number of presentations with SE and its associated costs, underlining the necessity to further evaluate the burden and optimize the treatment of SE.

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1. Introduction

In 2010 the European Brain Council commissioned a study to evaluate costs of disorders of the brain in Europe.¹ The number of people with epilepsy in Europe was estimated at 2,643,001 with mean annual costs of €-PPP 5221 (PPP = purchasing power parity, 2010 values) per person. Total direct and indirect costs would amount to €-PPP 13.8 billion. The authors stated that status epilepticus (SE) was an important source of direct costs, while noting the complete lack of cost-of-illness (COI) studies evaluating the costs related to SE in Europe.¹

Given the growing resource utilization and the increasing limitations of available healthcare resources, it has become essential to gather reliable cost estimates as a scientific basis for resource allocation and health policy decision-making. In fact, this

has become even more important as the introduction of new intravenous and oral antiepileptic drugs,² the rapid expansion of the elderly population and the use of alternative treatments in refractory SE³ may result in a considerable increase in costs or a shift in the distribution of cost components.^{4,5}

Costs caused by epilepsy and SE are closely related. Hospital costs may easily be attributed to epilepsy or SE alone. In contrast long-term sequelae as rehabilitation needs or indirect costs due to loss of productivity cannot be attributed without doubt to SE or epilepsy alone. Thus, the objective of this study was to determine and characterize the total epilepsy and SE related direct inpatient treatment costs. We also aimed to provide national estimates for the acute treatment of SE.

2. Patients and methods

In 2008 we performed a population-based COI study⁶ among adult patients with epilepsy in the district of Marburg–Biedenkopf (251,418 inhabitants according to the 2008 census, www.statistik-hessen.de). Only adults > 18 years of age were included and further

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data on direct and indirect cost were provided earlier in detail.⁶ The population structure in this district is representative of Germany and was used for a population-based estimate of the incidence of SE.⁷

This study was performed by means of a bottom-up approach from the perspective of the statutory health insurer and was granted approval by the local Ethics Committee.

Inpatient care is provided by three district hospitals without neurology departments and the multispecialty tertiary university hospital. The university hospital and two of the district hospitals provide accident and emergency care.

All four hospitals provided cost data on adult patients with a primary or secondary ICD-10 diagnosis of SE (G41.x) or epilepsy (G40.x) who were admitted during the study period of four months. The aim of this study was to calculate the genuine costs due to epilepsy or SE and not costs that may be triggered by other disease not related to epilepsy. Therefore the hospital billing data of each patient were crosschecked with patient files to determine whether or not the hospitalization was due to SE or epilepsy. The epilepsy diagnosis was based on the definitions proposed by the ILAE and the IBE.⁹ SE was defined as a single clinical seizure lasting >30 min or repeated seizures over a period of >30 min without intervening recovery of consciousness.^{7,10} Only admissions related to epilepsy or SE were evaluated and separated from admissions related to other causes like appendicitis or myocardial infarction when epilepsy was a co-morbidity. Admission due to acute symptomatic/provoked (i.e. alcohol withdrawal) seizures were not included. Hospital-based outpatient care, e.g. treatment in accident and emergency department with discharge on the same day, is reimbursed in Germany as outpatient treatment and was not evaluated in this study.

Inpatient costs were calculated according to German diagnosis related groups (G-DRG; www.g-drg.de).⁸ The costs were calculated in 2008 Euro (€) according to German recommendations for performing health economic evaluations as described in previous publications.^{6,11} The postal code of each patient's permanent address was used to identify patients living within and outside the district of Marburg–Biedenkopf in order to obtain a population-based estimate of the cost data.

Statistical analyses were performed using IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL, USA). Comparisons between groups were performed using the appropriate parametric and non-parametric tests.

3. Results

3.1. Patient population

During the 4-month study period 145 residents of Marburg–Biedenkopf were hospitalized with a primary or secondary ICD-10 diagnosis of SE or epilepsy. In 96 of these patients (96/145; 66.2%) admission was related to SE or epilepsy. In the other 49 cases epilepsy was a co-morbidity and was not related to the admission.

Table 1 shows the sociodemographic, clinical and cost characteristics of the patients with SE and of the control group (without SE) with newly diagnosed or established epilepsy. Thirteen (13.5%) patients were treated in the three district hospitals and 83 (86.5%) at the tertiary university hospital. All patients were treated only once during the study period.

Admission due to SE was seen in 10/96 patients (10.4%). Epilepsy was newly diagnosed in 30/96 patients (31.3%) and 5 of these patients presented with SE. Among the 61 patients with an established diagnosis the majority of 44 patients (44/61; 72.1%) were admitted due to seizures or side-effects of anticonvulsants, nine (9/61; 14.8%) required hospitalization due to seizure-related fractures and lacerations and six (6/61; 9.8%) were admitted for further diagnostics and treatment within the epilepsy surgery program.

3.2. Characteristics of patients with SE

Table 2 shows the clinical and treatment characteristics of patients with SE. SE was mainly focal (8/10), with (3/10) or without (5/10) secondary generalization. Fifty percent of the patients had a history of epilepsy at the time of the SE. Acute and remote stroke was the most common etiology in half of all patients. Benzodiazepines were used as first-line treatment in the prehospital phase in 6 out of 10 patients. Upon hospital admission benzodiazepines were administered in further three patients. In further course of treatment anticonvulsants were used in all patients, Table 2.

3.3. Inpatient costs

Table 1 shows the costs per hospital admission during the 4-month study period and annual cost estimates: costs of inpatient treatment of SE (€8347 ± 10,773 per patient per admission) were

Table 1
Sociodemographic, clinical and cost characteristics (2008 values).

		Status epilepticus n = 10	Newly diagnosed epilepsy# n = 25	Established epilepsy n = 61	All patients with SE and epilepsy n = 96
Age in years	Mean ± SD	73.0 ± 15.7	65.5 ± 20.4	54.7 ± 21.6	59.5 ± 21.6
	Median	77	71	49	65
	Range	36–91	23–96	21–93	21–96
Sex		% (n)	% (n)	% (n)	% (n)
	Male	70(7)	40 (10)	57.4 (35)	54.1 (52)
	Female	30(3)	60 (15)	42.6 (26)	45.8 (44)
Length of hospital stay in days	Mean ± SD	14.0 ± 13.0	5.4 ± 3.5	7.5 ± 7.3	7.6 ± 7.6
	Median	10.5	5	5	5
	Range	1–45	1–14	1–31	1–45
Costs per hospital admission	Mean ± SD	€8347 ± 10,773	€1998 ± 1089	€3475 ± 4413	€3607 ± 5171
	95% CI	€3565–16062	€1583–2438	€2463–4673	€2709–4710
	Minimum	€609	€520	€495	€495
	Median	€4702	€2098	€2098	€2204
	Maximum	€37,647	€4899	€23,145	€37,647
Costs during study period of 4 months		€84,366	€49,955	€211,998	€346,319
Proportion of total hospital costs		24.4%	14.4%	61.2%	
Estimated annual costs (district)		€253,098	€149,865	€635,994	€1,038,956
Estimated annual costs (Germany)		€83.4 Mio	€49.4 Mio	€209.5 Mio	€342.2 Mio

SD: standard deviation; #: without five patients with status epilepticus; SE: status epilepticus; 95% CI: 95% confidence interval using the bootstrap bias corrected and accelerated method.

Table 2
Clinical and treatment characteristics of patients with status epilepticus.

#	Age	Sex	Duration of hospital stay	Type of status epilepticus	Epilepsy diagnosis*	Etiologic factors	Treatment with BZP	AEDs used	Investigations	Concomitant diseases
1	36 y	m	1 d	Complex partial	Yes; FE	Low antiepileptic drug level, remote symptomatic	No	VPA, CBZ	CT	Perinatal hypoxia
2	62 y	m	19 d	Complex partial	No	Tumor	Yes, prehospital (MDZ)	LEV	CT, MRI, EEG	Brochial and hypopharynx carcinoma, alcohol abuse
3	64 y	m	4 d	Absence status	Yes	Medication induced	Yes (LZP)	VPA	CT, EEG	Schizoaffective disorder
4	74 y	f	10 d	Complex partial	No	Acute stroke (hemorrhage)	Yes (LZP)	LEV	CT, EEG	Dementia, diabetes
5	76 y	m	9 d	Secondarily generalized	Yes; FE	Remote stroke	Yes, prehospital (LZP; MDZ)	CBZ, LTG	CT, EEG	Diabetes
6	78 y	m	45 d	Simple partial	No	Tumor	Yes, prehospital (MDZ)	CBZ	CT, MRI, EEG	None
7	83 y	m	11 d	Absence status	Yes; IGE	Low antiepileptic drug level	Yes, prehospital (DZP)	LEV, PRM, TPM, ZNS	CT, EEG	Remote stroke, Binswanger's disease, coronary heart disease
8	83 y	f	11 d	Complex partial	Yes; FE	Remote stroke	Yes, prehospital (DZP)	LEV, TPM	CT, EEG	Dementia, diabetes, atrial fibrillation
9	83 y	f	25 d	Secondarily generalized	No	Remote stroke, Binswanger's disease	Yes (LZP)	LEV, TPM, VPA	CT, EEG, CSF	Dementia, aphasia, atrial fibrillation
10	91 y	m	5 d	Secondarily generalized	No	Remote stroke	Yes, prehospital (DZP)	VPA, LEV	CT, EEG, CSF	Pneumonia, diabetes, coronary heart disease

*Established epilepsy diagnosis prior to admission; BZP: benzodiazepine; FE: focal epilepsy; IGE: idiopathic generalized epilepsy; CBZ: carbamazepine, DZP: diazepam; LEV: levetiracetam; LTG: lamotrigine; LZP: lorazepam; MDZ: midazolam; PRM: primidone; TPM: topiramate; VPA: valproate; ZNS: zonisamide; CT: computed tomography; MRI: magnetic resonance imaging; CSF: cerebro-spinal fluid examination; remote: more than 7 days ago.

significantly higher than the inpatient treatment of patients with newly diagnosed ($\text{€}1998 \pm 1089$; $p = 0.014$) or established epilepsy ($\text{€}3475 \pm 4413$; $p = 0.026$). Treatment of SE associated with an acute illness and no previous diagnosis of epilepsy showed a tendency to higher costs ($\text{€}11,934 \pm 14,494$ per patient per admission) and duration of inpatient stay (20.8 ± 15.6 days) than the treatment of SE with a previous diagnosis of epilepsy ($\text{€}4938 \pm 4520$; $p = 0.420$; 7.2 ± 4.5 days; $p = 0.151$).

The costs of all inpatients treated for epilepsy or SE amounted to a total of $\text{€}346,319$ during the 4-month study period. Admission due to SE accounted for 24.4% of the total inpatient costs (total costs: $\text{€}84,366$). Hospital inpatient costs for patients without SE amounted to 14.4% ($\text{€}49,955$) for newly diagnosed epilepsy and to 61.2% ($\text{€}211,998$) for established epilepsy. In the latter group seizure-related injuries resulted in mean hospitalization costs of $\text{€}3399 \pm 1464$ (range 1364–5468) per patient per admission. Seven patients presented with seizure-related fractures of the skull, vertebra, maxilla, mandible, zygomatic bone and limbs; two patients had seizure-related lacerations requiring hospital admission. This resulted in total hospital costs of $\text{€}30,593$ (8.8% of the total inpatient costs). These patients had a mean length of hospital stay of 13.1 ± 8.1 days (median 12, range 1–26).

3.4. Annual costs estimations for the district and Germany

Based on these calculations we estimated the total annual hospital inpatient costs at $\text{€}1.038$ million in the district of Marburg–Biedenkopf.

Extrapolation of these cost data to the whole of Germany (population of 82 million) indicates that epilepsy causes direct hospital costs among adults of more than $\text{€}342$ million per year in Germany. SE is associated with hospital costs of $\text{€}83$ million, which far exceeds the costs for a newly established diagnosis of epilepsy, with a cost of $\text{€}49$ million. Seizure-related injuries resulted in inpatient costs of more than $\text{€}30$ million.

4. Discussion

This study is the first population-based evaluation addressing direct inpatient costs of adult patients with SE in Germany. We demonstrated that a relatively small number of patients with SE account for a high proportion (24.4%) of the overall inpatient costs related to epilepsy. The costs per admission due to SE were much higher than those of admissions due to newly diagnosed epilepsy or complications of established epilepsy.

The incidence of SE in the Caucasian population of industrialized countries is estimated at about 20 per 100,000 per year with a case fatality rate between 1.9 and 40%.¹² The Swiss EPSTAR study¹⁰ on age-specific annual incidence rates showed a bimodal distribution with a peak in children, a minimum during adolescence and young adulthood and a progressive increase in the elderly. The incidence rate was 38.7 per 100,000 in the age group between 0 and 4 years and decreased to 10.9 per 100,000 between 5 and 14 years of age.¹⁰ As the incidence rate sharply rises beyond age 60 (between 15.1 and 86 per 100,000)^{7,10,13,14}, the anticipated rapid growth of the elderly population will result in an increase of the economic impact of SE.

Only one other study in an academic hospital in Virginia looked into costs related to SE.¹⁵ The median reimbursement per patient admission was US\$8417 (1993/94 values) with an average length of hospitalization of 12.9 day. This is similar to the 14.0 days recorded in our study. Assuming 200,000 episodes of SE per year in all age groups, the authors projected SE-related hospital costs in the USA as high as \$4 billion per year. Our estimate of SE related annual hospital costs of $\text{€}83$ million in adults is based on a region with an incidence of 15.8–17.1/100,000 inhabitants⁷ with 11,000–12,000 affected adults per year in Germany. This incidence rate is considerably lower than that estimated in the population of Richmond, Virginia (41/100,000).¹³

Inpatient costs for the treatment of SE in Germany ($\text{€}8347$ per admission) are comparable to inpatient costs for the treatment of a first-ever-in-a-lifetime ischemic stroke ($\text{€}6731$ in 2004).¹⁶ The total national costs attributable to inpatient treatment for ischemic

stroke have been estimated at €1.6 billion per year.¹⁶ Our national cost estimate for the total inpatient treatment costs of epilepsy and SE amount to €342 million per year.

We aimed to provide population-based estimates for the district of Marburg–Biedenkopf. Using a study design with the evaluation of district residents only in all four hospitals serving the district, we were able to enroll a representative cohort of patients. Using estimates based on incidence studies,^{7,17} 11 adult patients with SE and 33 patients newly presenting with epilepsy would be expected to be seen in the hospitals in the district during the 4-month study period. The fact that we were able to enroll 10 patients with SE and 30 newly diagnosed patients suggests a good data capture for this study.

Despite the careful study design, this COI study suffers from certain limitations inherent to such investigations. Although the population structure was considered representative of Germany, we cannot exclude the possibility that patterns of epilepsy care may differ in other rural or urban parts of Germany. We cannot exclude an under-ascertainment of costs as we did not evaluate residents with SE or epilepsy treated outside the district. Also, for better comparison, we used a definition of SE used in epidemiological studies not mirroring clinical practice, where a generalized tonic–clonic seizure lasting for more than 5–10 min would usually be considered as SE and treated as such. As we did not include children and adolescents with SE in this study, we cannot provide cost estimates in this important patient group with a high incidence of SE. Furthermore, the reimbursement system in Germany relies on diagnosis related groups and may be not representative for other countries using daily charges.⁸ It also remains possible that the introduction of a DRG-based reimbursement affects the choice of treatment setting in favor of hospital admissions.¹⁸ Overall, it remains difficult to distinguish costs due SE and other associated acute illnesses as stroke or tumor. The relatively short evaluation period of 4 months could have led to a relatively high variability in cost estimates.

Future evaluations should focus on the longitudinal economic impact of SE, which will provide important information on the costs of sequelae of SE. These evaluations should include direct costs for inpatient treatment, rehabilitation and subsequent outpatient care as well as indirect costs for loss of earning of patients and carers. In addition, further studies are warranted to answer questions regarding the cost-effectiveness of different treatment options in SE.

Conflict of interest statement

Dr. A. Strzelczyk has received travel support and honoraria from Desitin, Eisai and UCB Pharma. Dr. S. Knake has served on the speakers' bureau of Desitin and Eisai. Dr. W.H. Oertel has received honoraria and/or research grants from Boehringer Ingelheim, Desitin, GlaxoSmithKline, Merck, Mundipharma, Novartis, Orion, Sharp & Dohme, Schwarz Pharma Neuroscience/UCB Pharma, Synosia and Teva. Dr. F. Rosenow has received honoraria as scientific advisor from GlaxoSmithKline, Eisai, UCB Pharma and Pfizer. He has received speaker honoraria from UCB Pharma, GlaxoSmithKline, Eisai, Desitin, Medtronic and educational grants from Nihon-Kohden, UCB Pharma, Medtronic, Cyberonics and Cerbomed. Dr. H.M. Hamer has served on the scientific advisory

boards of Eisai, Pfizer and UCB Pharma. He has served on the speakers' bureau of Desitin, Eisai, GlaxoSmithKline and UCB Pharma and received research funding from Desitin, Janssen-Cilag, GlaxoSmithKline and UCB Pharma.

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