THE NORTH LONDON CONVULSIVE STATUS EPILEPTICUS IN CHILDHOOD SURVEILLANCE STUDY: NLSTEPSS

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For Mandy and our beautiful Sophie,

Your love, patience and understanding surpass my understanding.

You bring sunshine in my life and inspire me.....

Abstract

Convulsive status epilepticus (CSE) is the most common medical neurological emergency in childhood. To ultimately improve the management of CSE, an understanding of its incidence, aetiology, seizure types, treatment and outcome in the general childhood population is required.

Using emerging techniques for systematic reviews in observational studies, a systematic review of the epidemiology of status epilepticus was conducted. All eligible studies were based on predominantly or exclusively adult populations. The data from these studies suggest that the epidemiology of CSE in childhood differs from that in adults. Thus, an epidemiological study on CSE in a paediatric population was required. The North London convulsive STatus EPilepticus in childhood Surveillance Study (NLSTEPSS), a prospective study, is the first such study.

In NLSTEPSS, children with CSE were identified through a multi-tiered notification system. Data were collected using a standard questionnaire and capture-recapture was used to assess ascertainment. The incidence of CSE in childhood is 18-20/100,000/year (95% CI 17- 23/100,000/yr), with a higher incidence amongst non-white children, children of lower socioeconomic status and younger children. Lack of prehospital treatment, and treatment with more than 2 doses of benzodiazepines independently increase the likelihood of CSE lasting longer than 60 minutes.

A third of children with CSE are not given prehospital treatment and only 21% of those treated are given adequate initial doses. Treatment with more than 2 doses of benzodiazepines is associated with respiratory depression. Intravenous lorazepam may be better first line therapy than rectal diazepam and intravenous phenytoin may be better second line therapy than rectal paraldehyde.

CSE lasting longer than 60 minutes and CSE associated with respiratory depression independently increase the likelihood of admission to paediatric intensive care (PICU). Thus, strategies to reduce those factors may reduce admissions to PICU.

On the basis of the data from NLSTEPSS, treatment guidelines for CSE in childhood may need to be revised and a new treatment guideline is proposed.

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PERSONAL CONTRIBUTION OF THE CANDIDATE

In addition to involvement in the design and implementation of the studies in this thesis, the specific personal contributions of the candidate to each chapter are detailed below.

Chapter 1	Literature review
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	Development of scoring system for systematic review
	Systematic review of literature
Chapter 3	Literature review
Chapter 4	Literature review
	Formation of research collaborative network
	Formation of steering group
	Design and implementation of telephone notification system
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Chapter 7	Design of data collection proforma
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	Collection of data
	Review of patient and clinical data
	Statistical analysis

PUBLICATIONS ARISING FROM THIS THESIS

Peer reviewed papers

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2. **Chin R.F.**, Neville B.G., Scott R.C. A systematic review of the epidemiology of convulsive status epilepticus. *European Journal of Neurology* 2004; 11(12): 800-810 *(CME article).*

3. **Chin R.F.**, Verhulst L., Neville B.G., Peters M.J., Scott R.C. Inappropriate emergency management of status epilepticus in children contributes to need for intensive care. *Journal of Neurology, Neurosurgery and Psychiatry* 2004; 75:1584-1588 *(Featured in Archives of Diseases in Childhood Education and Practice Journal, 2004; 89:ep45).*

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1. **Chin R.F.**, Neville BGR, Peckham C, Bedford H, Wade A, Scott RC, *for the NLSTEPSS Collaborative Group.* The incidence, aetiology, seizure characteristics, recurrence, and mortality of convulsive status epilepticus in childhood in North London.

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3. **Chin R.F.**, Neville BGR, Peckham C, Bedford H, Wade A, Scott RC, *for the NLSTEPSS Collaborative Group.* Determinants of duration of convulsive status epilepticus in childhood.

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Poster presentations

1. **Chin R.F.**, Neville BGR, Peckham C, Bedford H, Wade A, Scott RC, *for the NLSTEPSS Collaborative Group.* An analysis of first and second line agents for the treatment of convulsive status epilepticus in childhood. *Developmental Medicine and Child Neurology* 2005;47(supplement 101):7. (One of 10 posters selected to be presented orally - British Paediatric Neurology Association)

2. **Chin R.F.**, Neville BGR, Peckham C, Bedford H, Wade A, Scott RC, *for the NLSTEPSS Collaborative Group.* The epidemiology of convulsive status epilepticus in childhood. *Developmental Medicine and Child Neurology* 2004; 46:98. (British Paediatric Neurology Association)

3. **Chin R.F.**, Peters M., Verhulst L., Donati-Genet P., Scott R.C. Focal onset of status epilepticus is common, and frequently associated with an acute neurological insult: lessons from a PICU. *Pediatric Critical Care Medicine* 2003; 4(3)Suppl:A89. (International Congress of Paediatric Intensive Care)

4. **Chin R.F.**, Verhulst L., Donati-Genet P., Scott R.C., Peters M. APLS guidelines for management of convulsive status epilepticus are not followed in the most severe cases. *Pediatric Critical Care Medicine* 2003; 4(3) Suppl:A176. (International Congress of Paediatric Intensive Care)

5. Scott R.C., **Chin R.F.**, Neville B.G., Peckham C., Bedford H., Wade A. NLSTEPSS - A population-based study on convulsive status epilepticus in childhood. *Developmental Medicine and Child Neurology* 2003; 45:22. (British Paediatric Neurology Association)

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GLOSSARY

95% CI	95% confidence interval
A&E	Accident and Emergency Department
ABM	Acute bacterial meningitis
AED	Anti-Epileptic Drug
APLS	Advanced Paediatric Life Support
AUDIT	Identified through audit of hospital admissions
BPNA	British Paediatric Neurology Association
BPSU	British Paediatric Surveillance Unit
CATS	Children's Acute Transport Service
CNS	Central nervous system
CSE	Convulsive Status Epilepticus
ED	Census Enumeration District
FORM	Identified through regional BPSU-like surveillance scheme
GOSH	Great Ormond Street Hospital for Sick Children
ICD	International Classification of Diseases
ILAE	International League Against Epilepsy
IMD 2000	Indices Multiple of Deprivation 2000
IMD 2004	Indices of Multiple Deprivation 2004
LAS	London Ambulance Service
LP	Lumbar puncture
NCSE	Non-Convulsive Status Epilepticus
NLSTEPSS	North London convulsive Status Epilepticus in childhood Surveillance Study
ONS	Office of National Statistics
PFS	Prolonged Febrile Seizure
PHONE	Identified through telephone notification
PICU	Paediatric Intensive Care Unit
SAS	Small Area Statistics
SE	Status Epilepticus
SMR	Standardised Mortality Ratio
SOA	Super Output Area
Study ID	Study identification number

PART ONE

INTRODUCTION/ BACKGROUND

CHAPTER ONE: INTRODUCTION

1.1 Aims of the study

Status epilepticus is the most common medical neurological emergency in childhood (Delorenzo et al. 1995, Hesdorffer et al. 1998) and may be convulsive or non-convulsive in nature. Most available data on status epilepticus were obtained from either hospital-based or tertiary clinic series resulting in biased information that may not be applicable to the general childhood population. In order to ultimately improve the management of convulsive status epilepticus (CSE) in childhood, an understanding of the epidemiology of CSE in the general childhood population is required. This thesis will attempt to advance the understanding of status epilepticus in the general childhood population by providing population based estimates of the incidence, aetiology, seizure characteristics, treatment and short term outcome of convulsive status epilepticus in a paediatric population.

1.2 Historical perspective

The probable first documented clinical description of CSE is found on the Sakkiku cuneiform which dates from 718-612 BC. That description concludes with a statement suggesting that CSE may be fatal but there was no suggestion that CSE originated from the brain. From then until the Renaissance in the 16th century, there is little mention of CSE in any medical literature. In 1586, Gavassetti observed that the brain of cardinal Commendoni was swollen and its ventricular system dilated following fatal SE that had lasted 24 hours. The brain was identified as the origin of CSE in the description by Thomas Willis in the Pathologicae Cerebrae in 1667. Until the work of Louis Calmeil and Désiré-Magloire Bourneville at the Salpetriere,

the biggest asylum in Europe and its sister institution the Bicetre in the mid 19th century, SE was largely considered as a single condition characterised by generalised tonic clonic seizures. The term "etat de mal" was coined by the patients of these institutions themselves and is first found in Calmeil's thesis. The latinised English version of this expression, status epilepticus, was first used in Bazires translation of Trousseau's lectures on clinical medicine (Shorvon 1994a). Since the early restrictive conception of SE, it has become clear that SE is not a single condition and there are now many clinical descriptions of different types of SE.

1.3 Definition of SE

It is widely acknowledged that generalised tonic-clonic CSE is a common medical neurological emergency requiring prompt, adequate and appropriate treatment. Its diagnosis is usually not difficult except in patients in whom the seizures are prolonged and whose clinical features become increasingly attenuated (Lowenstein and Aminoff 1992; Treiman 1995). There remains some debate on the most appropriate emergency treatment of CSE, particularly on the role of prehospital treatment, the route of administration and choice of drugs. Although there are consensus views on the emergency management of CSE worldwide, these differ from one another (Epilepsy Foundation of America's Working Group on Status Epilepticus 1993; Emergency Paediatrics Section 1996; O'Regan et al. 1996; Treiman et al., 1998; Scott et al. 1999; Appleton et al. 2000). There remains some debate on the definition of status epilepticus.

In the first International Classification of Epileptic Seizures that was developed by the International League Against Epilepsy (ILAE) in 1964, status epilepticus was defined as " a seizure that persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring epileptic condition" (Commission on the Terminology of the International League Against Epilepsy 1964). This definition was retained unchanged in the revised classification published in 1970 (Gastaut 1970) and remains the official definition of SE by the World Health Organisation. The definition was modified slightly in 1981 to refer to that situation in which " a seizure persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur" (Commission on the Terminology of the International League Against Epilepsy 1981). Status epilepticus has been described as "the maximum expression of epilepsy" (Shorvon 1994b). In pathophysiological terms, SE can be defined as a condition in which there is failure of the usual mechanisms that terminate seizures but currently there is limited understanding of those mechanisms and this definition is not clinically useful. These definitions can be considered inadequate as they all lack a specific duration of seizure activity and thus do not clarify when a short seizure becomes SE.

1.3.1 Definition for epidemiological, pathophysiological and outcome purposes

The most common duration of seizure activity qualifying as SE has been 30 minutes, leading to the commonly used definition " a seizure or series of seizures which last for 30 minutes or more without full recovery of consciousness between the seizures" (Celesia 1976; Brodie 1990; Shepherd 1994). The basis of this duration has been rooted in the seminal work of Meldrum and colleagues in the 1970's where 30 minutes reflects a time during which ongoing seizures can cause

neuronal injury in animal models (Meldrum et al. 1973). In addition to the work of Meldrum and colleagues, other animal data suggest that seizures need to last at least thirty minutes for neuronal damage to occur (Lemos et al., 1995; Fujikawa 1996). For epidemiological, pathophysiological and outcome purposes, a definition that includes a duration of seizures lasting at least thirty minutes is therefore appropriate in order to identify those patients at risk of brain injury.

1.3.2 Definition for treatment purposes

It is not ethical to wait for at least 30 minutes of seizure activity before initiating treatment and in order to prevent permanent neurological sequelae that may arise from seizure activity lasting at least thirty minutes, for treatment purposes, a much shorter duration of seizure activity qualifying as status epilepticus may be appropriate. In a review on the treatment of SE published in 1991, Bleck defined SE using a duration of at least 20 minutes (Bleck 1991). In the Veterans Affairs Cooperative Trial on Treatment of Generalised Convulsive Status Epilepticus, SE was defined using a duration of at least 10 minutes (Treiman et al., 1998). The results of two more recent studies suggest that the most appropriate treatment definition time may be even shorter than those previously used. Although most seizures spontaneously terminate within five minutes of their onset, the majority of seizures that last longer than five minutes, are unlikely to stop spontaneously within the next few minutes and will continue for at least 30 minutes (DeLorenzo et al., 1999; Lowenstein et al., 1999; Shinnar et al., 2001a). It may therefore be argued that patients who have a seizure lasting 5 minutes are already likely to have failure of the usual mechanisms of seizure termination and are in the early stages of SE. Thus, for treatment purposes, a definition of SE stating a time of at least 5 minutes may be appropriate. As increasing seizure duration is associated with increasing

difficulty in seizure termination (Knudsen 1979; Shinnar et al., 2001a), the period immediately following the five minute duration threshold provides a window of opportunity in which rescue therapy may be given and work but within which rescue failure may also be anticipated and planned for. The results of a study of 44 children with 58 episodes of generalised seizures by Knudsen, suggest that in children, the optimum period for initiation of rescue therapy may be within 15 minutes of the onset of the seizure, as children treated within 15 minutes of the onset of the seizure were more likely to have seizure termination than those treated after 15 minutes (Knudsen 1979). Figure 1.1 summarises duration of seizure activity against key time periods in the natural history of a seizure.

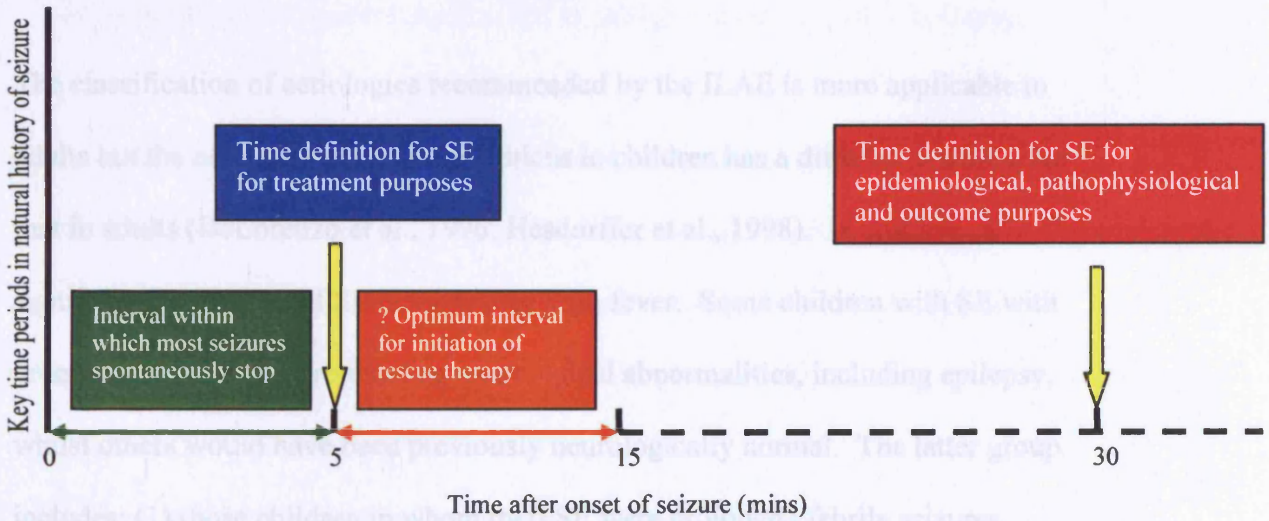

Figure 1.1: Duration of seizure activity against key time periods in the natural history of a seizure.

Thus, all the above definitions of SE are suitable in different situations, but there is none that is ideal for every situation. In an attempt to overcome the problems with previous definitions, Shorvon has proposed that SE be defined as "a condition in which epileptic activity persists for 30 minutes or more, causing a wide spectrum of clinical symptoms and with a highly variable pathophysiological anatomical and aetiological basis (Shorvon 1994b)." Although it addresses some of the problems

with prior definitions, it is still not suitable for all situations. It is likely that different definitions of SE will be required for different settings. This thesis aims to characterise the epidemiology of CSE in childhood and thus, a definition that includes seizures lasting at least thirty minutes will be used.

1.4 Aetiology of SE

There is good evidence from epidemiological studies and clinical series that aetiology of SE is an important determinant of the outcome of patients with SE and it is therefore important to identify the causes of SE. A classification of status epilepticus according to aetiology recommended by the ILAE is listed in Table 1.1

The classification of aetiologies recommended by the ILAE is more applicable to adults but the aetiology of status epilepticus in children has a different profile from that in adults (DeLorenzo et al., 1996; Hesdorffer et al., 1998). In children, a significant proportion of SE is associated with fever. Some children with SE with fever would have had pre-existing neurological abnormalities, including epilepsy, whilst others would have been previously neurologically normal. The latter group includes: (1) those children in whom their SE were prolonged febrile seizures, defined as SE in a previously neurologically normal child aged between 6 months and five years during a febrile (temperature above 38 ^{0}C) illness in the absence of defined central nervous system (CNS) infection (Scott et al., 2002; Scott et al., 2003) and (2) children with acute symptomatic SE due to CNS infections. Results from epidemiological studies and thus less likely to be subject to referral bias, suggest that prolonged febrile seizures are associated with low morbidity and mortality (Nelson and Ellenberg, 1978; Maytal et al., 1990; Hesdorffer et al., 1998).

1. Acute symptomatic - SE in a previously neurologically normal child, within a week of an underlying aetiology including CNS infection, prolonged febrile seizures, encephalopathy, head trauma, cerebrovascular disease and metabolic or toxic derangements.

2. Remote symptomatic - SE in the absence of an identified acute insult but with a history of a pre-existing CNS abnormality more than 1 week before.

3. Idiopathic Epilepsy related - SE that is not symptomatic and occurred in children with a prior diagnosis of idiopathic epilepsy or when the episode of SE is the second unprovoked seizure that has led to a diagnosis of idiopathic epilepsy.

4. Cryptogenic Epilepsy related - SE that is not symptomatic and occurred in children with a prior diagnosis of cryptogenic epilepsy or when the episode of SE is the second unprovoked seizure that has led to a diagnosis of cryptogenic epilepsy.

5. Unclassified - SE that cannot be classified into any other group.

Table 1.1: International League Against Epilepsy's recommended classification of SE according to aetiologies (Gastaut 1983; International League Against Epilepsy 1993).

A classification system, such as that recommended by the ILAE, that includes prolonged febrile seizures in the same category as SE due to an identified acute neurological insult, such as acute bacterial meningitis, may be inappropriate for paediatric epidemiological or outcome studies. The results of studies that use such a

classification system may erroneously amplify the severity of outcome of prolonged febrile seizures and conversely, dilute the severity of acute neurological insults. In addition, the precise pathophysiological mechanisms for prolonged febrile seizures are unknown but there is evidence of age and genetic influences (Annegers et al., 1987; Offringa et al. 1991; Hauser 1994; Berg et al. 1996; Corey et al. 2004). In order to identify factors associated with prolonged febrile seizures that may lead to pathophysiological hypotheses on the mechanisms for prolonged febrile seizures, including the genetic mechanisms, perhaps an attempt to identify prolonged febrile seizures as a distinct category of status epilepticus should be made. A revised classification system of the aetiologies of SE, with prolonged febrile seizures as a distinct category, may be more applicable to paediatric studies whilst retaining the flexibility to present data in keeping with the current ILAE guidelines and thereby facilitate comparison with other studies. Nonetheless, such a revised classification would still have its limitations as accurate categorisation of individual cases may depend on the degree of investigation, the availability of ancillary tests and clinical data. Accurate diagnosis may require state of the art technology and procedures. For example, in the absence of a diagnostic lumbar puncture, it may be difficult to establish whether a ten month old previously neurologically normal child presenting with SE associated with fever and categorised as having a prolonged febrile seizures, should have been categorised as acute symptomatic SE. It is also possible that an eight month old child presenting with afebrile SE may have a focal area of cortical dysplasia and not have any further seizures or may have had the initial presentation of epilepsy with severe myoclonic epilepsy of infancy with frequent episodes of SE.

1.5 Other classifications of status epilepticus

Status epilepticus may be classified as convulsive or non-convulsive in nature.

1.5.1 Definition of Convulsive Status Epilepticus (CSE)

Convulsive status epilepticus is defined as a seizure with focal or generalised motor manifestations, or series of such seizures between which consciousness is not regained, which last for at least 30 minutes (Commission on the Terminology of the International League Against Epilepsy 1981; International League Against Epilepsy 1993).

Episodes of convulsive status epilepticus may be further subcategorised according to seizure types and whether the episodes were intermittent or continuous in character.

1.5.1.1 Convulsive Status Epilepticus (CSE) and Seizure Types

Based on the criteria of the International League Against Epilepsy, convulsive status epilepticus may be defined as: primary generalised, focal with secondary generalisation and focal (International League Against Epilepsy 1993; Engel 2001). CSE seizure types that may be subtyped into tonic, clonic and tonic-clonic seizures.

1.5.1.2 Intermittent or Continuous Convulsive Status Epilepticus (CSE)

Episodes of CSE that are a single continuous seizure may be characterised as continuous CSE, and episodes that are serial seizures without recovery of consciousness between seizures may be characterised as intermittent CSE.

1.5.2 Definition of Non-Convulsive Status Epilepticus (NCSE)

Whilst a clear and widely recognised clinical/EEG definition for non-convulsive status epilepticus has not been established, a working definition has been multiple seizures or continuous seizure activity on EEG with cognitive or behavioural change unaccompanied by frank convulsive movements (Kaplan 2003).

1.6 Outcome of Status Epilepticus from Hospital based studies

1.6.1 Definition of hospital based studies

Hospital based studies may be defined as studies conducted in single hospitals or networks of hospitals over a wide geographic region without well defined study populations (Kilgore and Nyambat 2004).

1.6.2 Outcome of SE from Paediatric Intensive Care Unit (PICU) based studies

Most of what is known about SE is derived from hospital-based studies. Despite this, studies on the admission to paediatric intensive care for status epilepticus i.e. the most severe end of the spectrum are very limited. In the only published study, a Canadian study, 147 children (1.6% of all admissions) were admitted to PICU for or with SE, over a ten year period (Lacroix et al., 1994). Most cases (79%) occurred in children who had been previously neurologically normal but had an acute neurological insult resulting in SE. Case fatality during hospitalisation was 6%, but 9% within one year of onset of SE. However, of the 114 children who were previously neurologically normal, neurological sequelae ranging from minor neurological and/or neurodevelopmental impairment to persistent vegetative states were identified in about a third (32%) of patients at discharge. At one year 23% still showed some deficit (Lacroix et al., 1994).

1.6.3 Outcome of SE from Non-PICU, hospital based studies

There have also been estimates of morbidity and mortality from hospital based studies that were not PICU based. In their retrospective review of 239 episodes of status epilepticus admitted to a tertiary institution, Aicardi and Chevrie identified physical and cognitive problems in 53% of children following SE (Aicardi et al., 1970). Other studies estimate the risk of partial or generalised epilepsy following SE to be between 19% and 82% (Yager et al., 1988; Maytal et al., 1989; Shorvon 1994b). Mortality in the Aicardi series was 11% (Aicardi et al., 1970) but subsequent studies have reported a lower mortality of between 2.3 and 6% (Celesia 1983; Maytal et al., 1989; Phillips and Shanahan 1989). Some of this apparent reduction in mortality may have been due to a change in the definition of SE. Data from animal studies (Meldrum et al. 1973; Lemos et al., 1995; Fujikawa 1996) and hospital based studies (Aminoff et al. 1980; Towne et al., 1994; Sagduyu et al., 1998) suggest that mortality increases in proportion to seizure duration. In the Aicardi study SE was defined as seizure activity lasting at least 60 minutes compared to more recent studies that used 30 minutes within their operational definition. It is also possible that the apparent reduction in mortality may be partially attributed to improved treatment of status epilepticus (International League Against Epilepsy 1993) as well as inexplicable changes in disease mortality with time.

Hospital based studies have suggested that age, duration of SE and aetiology are the major determinants of morbidity and mortality from SE (Aicardi et al., 1970; Rowan and Scott 1970; Dunn 1988; Maytal et al., 1989; Phillips and Shanahan 1989; Gross-Tsur and Shinnar 1993; Shorvon 1994b; Towne et al. 1994). Several

such studies have reported that death and neurological sequelae are more common in the two extremes of age, those less than three years of age and those older than 60 years (Dunn 1988; Maytal et al., 1989; Gross-Tsur and Shinnar 1993). Two of these studies reported that this observation may have been primarily due to an increased proportion of acute symptomatic SE in the extremes of age since there was no difference within age groups of the outcome amongst other aetiologies (Maytal et al., 1989; Gross-Tsur and Shinnar 1993). Two hospital-based studies identified duration of seizures as important determinants of outcome (Rowan and Scott 1970; Dunn 1988). In their case series of 42 patients, Rowan and Scott reported that status epilepticus that lasted a mean of 1.5 hours were not associated with any residual neurological deficit, episodes lasting 10 hours were associated with neurological sequelae and episodes lasting 13 hours were associated with death. Dunn reported that duration of seizures were twice as long in those patients who died or who were left with residual neurological deficit (mean duration 3.9 hours) compared to patients with no new neurological deficits. There is also evidence that children whose status epilepticus is caused by acute neurological insults and those with progressive neurological abnormalities have the worst prognosis (Phillips and Shanahan 1989; DeLorenzo et al., 1992; Gross-Tsur and Shinnar 1993; Shorvon 1994b; Towne et al. 1994).

Thus, hospital based studies suggest that SE is potentially harmful. However, in order for institutions, and even governments, to make decisions on allocation of resources that may be used to develop primary and secondary preventative strategies for SE, data on the frequency, aetiology and morbidity and mortality associated with status epilepticus in the general population are required.

CHAPTER 2: A SYSTEMATIC REVIEW OF THE INCIDENCE, AETIOLOGY AND OUTCOME OF STATUS EPILEPTICUS

Through a systematic review, the candidate aimed to assess the methodological quality as well as similarities and differences between available population based studies in order to assimilate available data to clarify the epidemiology of SE.

2.1 Systematic reviews and observational studies

A systematic review was conducted in order to minimise bias and random errors, while at the same time producing an accurate summary of all available data. In general, there is a vast amount of original research on any one subject published each year and studies vary in their methodology, sample size, quality and results. It is therefore difficult to keep abreast of and to synthesize all available information on a body of research. A systematic review entails a structured approach to identifying, assessing, synthesizing and combining the results of all relevant studies to make conclusions about a body of research. Without such a systematic approach, a review, while potentially useful, may be incomplete and may comprise only data previously known to the reviewer (Mulrow 1987; Elbourne et al. 1989; Chalmers et al. 2002). Some reviewers may be experts in a particular subject, but not be well informed about other related subjects. This will result in a final review that may be biased towards personal knowledge but not necessarily an accurate summary of all available data on the subject.

On the whole, systematic reviews have been conducted for randomised controlled trials (RCTs) as RCTs have long been viewed as the "gold standard" of evidence for intervention studies; observational studies have been largely overlooked. This has resulted in the development of methodology for systematic reviews mainly for RCTs. However, in some situations, only data from observational studies, such as non-intervention epidemiological studies, are available, possible or appropriate (Berlin 1995). To illustrate this, observational studies have been used to evaluate educational programmes (Sipe and Curlette 1997) and assess risk factors for disease (Ioannidis and Lau 1999). Studies on the latter may not be randomised because the risk factors may be related to intrinsic human practices and it is unethical to expose subjects to harmful risk factors (Lipsett and Campleman 1999). Thus, there is increasing recognition that observational studies provide useful evidence, resulting in more recent, active development of methodologies for systematic reviews of observational studies (Mulrow et al., 1997; Sutton et al., 1998; Stroup et al., 2000) and recently, there have been several systematic reviews of qualitative studies (Bahtsevani et al., 2004; Gruenewald et al., 2004; Milton et al., 2004; Walter et al., 2004; Donald et al., 2005).

2.2 Aim of the systematic review

The specific aim of this systematic review is to identify and synthesize all available population based data on SE to arrive at conclusions on the epidemiology of SE including:

- The incidence of SE and the effect of gender, ethnicity and age on incidence.
- The range of aetiologies of SE, including the association of SE with epilepsy
- The recurrence of SE
- The mortality associated with SE

In addition, the systematic review will highlight deficiencies in knowledge on status epilepticus that may be addressed in subsequent studies.

2.3 Methods

2.3.1 Search Strategy

A systematic search for ascertainment of appropriate articles was conducted using the recommendations of the NHS Centre for Reviews and Dissemination (NHS Centre for Reviews and Dissemination 2001). For details of the search strategy, see Table 2.1.

Step 1: Computer assisted literature searches of the bibliographic databases: Medline, Cochrane Collaboration database, Embase, Web of Science and CINALH for papers published between 1966 and November 2002 using the following search terms:

- Status epilepticus and population*
- Status epilepticus and epidemiology
- Status epilepticus and incidence
- Status epilepticus and aetiolog*
- Status epilepticus and etiolog*
- Status epilepticus and cause*
- Status epilepticus and seizure type
- Status epilepticus and mortality
- Status epilepticus and fatality

All of the above searches were repeated with prolonged febrile convulsion* or prolonged febrile seizure* instead of status epilepticus.

All the searches were combined with (or stepwise limits conducted in Medline):
(i) review (ii) meta-analysis

Step 2: The reference list of articles identified in step 1 was examined to identify additional relevant studies.

Step 3: An internet search up to December 31, 2003 using Google as the search engine using the search strategy in Step 1 was conducted.

Step 4: The conference proceedings and abstracts of the British Paediatric Neurology Association (BPNA), the American Epilepsy Society (AES) and European Paediatric Neurology Society (EPNS) Year 1995 to Year 2003 were handsearched.

Table 2.1: Search strategy for population based studies on status epilepticus.

2.3.2 Selection criteria

All population-based studies on status epilepticus where the primary outcome was incidence, aetiology, seizure types or mortality of SE were included. Studies of all age groups were included. Studies that were based in a single institution or did not involve a network of hospitals serving a well-defined general population and non-primary studies were excluded.

2.3.3 Data extraction and assessment of Study Quality

Data to be extracted were agreed by the candidate and one of the candidate's supervisors, and included study period, details of the study population, selection criteria, definitions, classification of seizure types, validation of the databases and outcome measures. The candidate extracted the data using a data extraction form and a second reviewer confirmed them. To assess methodological quality, the candidate developed a scoring system based on a published proposal for reporting meta-analysis of observational studies (Stroup et al., 2000) and the guidelines for epidemiologic studies on epilepsy of the International League Against Epilepsy (International League Against Epilepsy 1993) (see Table 2.2). Each study was scored on the following items: type of study design, description of study population, adequacy of case definitions, selection criteria of study population, definition of seizure types and aetiologies according to the ILAE guidelines, adequacy of definition of outcome measures, type of rate/effect/impact and whether there were adjustments for degree of ascertainment. In accordance with the ILAE guidelines for epidemiologic studies on epilepsy, the more important determinants of quality were considered to be type of study design, definitions of cases and outcomes, classification of seizure type and adjustment of rates. Thus, these items were given greater scores. Using the scoring system, each study was assessed independently by

the two reviewers. Inter-rater agreement (kappa scores) for assessment of quality of study methodology was determined for each study.

Study Design	12 = Prospective 5= Retrospective
Sample Size	2= Clearly defined 1= Unclearly defined 0= Not defined
Methodological definitions in Individual studies	4= All clear 2= Most clear 1= Most not clear
Inclusion criteria for selection of cases of SE from study population	4= Clear 2= Unclear 1= Not defined
Seizure type defined according to the ILAE guidelines?	4= Clear 2= Unclear 1= No
Risk factors/ aetiology defined according to ILAE guidelines?	4= Clear 2= Unclear 1= No
Definitions of outcome parameters	2= All clear 1= Unclear 0= Most not clear
Standardization of rates/ratios	4= Either age-specific/ age-adjusted/ sex- specific 2= Age-specific /age- adjusted/ sex-specific 1= Crude only
Ascertainment adjustment	4= Clear 1= Unclear/None

Table 2.2: Scoring system for assessment of methodological quality of population based studies on SE. Maximum score = 40, minimum score = 11.

2.4 Results

There were neither systematic reviews nor meta-analyses. Six population-based projects on status epilepticus (Richmond Group, Virginia, USA; Rochester Group, Minnesota, USA; French speaking Cantons Group, Switzerland; Hessen Group, Germany; California Group, USA; St. Louis Group, USA) yielding nine published reports (DeLorenzo et al., 1995; DeLorenzo et al., 1996; Logroscino et al., 1997; Hesdorffer et al., 1998; Coeytaux et al., 2000; Knake et al., 2001; Logroscino et al., 2002; Wu et al., 2002) and three abstracts (Morton et al., 2001; Towne et al. 2002; Trevathan et al., 2002;) fulfilled the inclusion criteria for entry into the review. Four projects were conducted in the USA, three of which were retrospective (Rochester, California, St. Louis Groups) and one was prospective (Richmond Group). The remaining two population-based projects were European based and prospective (Hessen Group and the French speaking Cantons Group). All studies were conducted after the ILAE's guidelines for epidemiologic studies were published. The results are presented for data collection up to December 31, 2003. Studies were pooled only when their definitions of relevant variables were similar or the results could be processed and analysed as such. For a glossary of definitions used in the studies, see Appendix 1.

2.4.1 Description of the Studies

The description of the studies, methodological quality scores and inter-rater agreement are shown in Table 2.3. The quality scores ranged from 19-34 out of a possible maximum of 40. Inter-rater agreement was good to very good with kappa scores between 0.67 - 1.0.

Studies	Country	Design	Sample Size	Methods definitions	Inclusion criteria	ILAE SE type	ILAE Aetiology	Outcome	Standardization of Rates / Ratios	Ascertainment Adjustment	Methodology Score	κ
PUBLISHED PAPERS												
DeLorenzo 1995	USA	Prospective	137 adults, 29 children	Most Clear	Unclear	Clear	Unclear	Clear	Age-specific	Clear	32	0.67
DeLorenzo 1996	USA	Prospective	137 adults, 29 children	Most Clear	Unclear	Clear	Unclear	Clear	Age-specific	Clear	32	0.67
Logroscino 1997	USA	Retrospective	132 adults ,52 children	Most Clear	Clear	Clear	Clear	Clear	Age- and sex-specific	No	28	1.0
Hesdorffer 1998	USA	Retrospective	130 adults, 69 children	Most Clear	Clear	Clear	Clear	Clear	Age- and sex-specific	No	28	1.0
Waterhouse 1999	USA	Prospective	433 adults, 212 children	Most Clear	Clear	Clear	Unclear	Clear	Crude	Unclear	31	0.89
Coeytaux 2000	Switzerland	Prospective	108 adults, 64 children	Most Clear	Unclear	Clear	Unclear	Clear	Age- and sex-specific	No	31	1.0
Knake 2001	Germany	Prospective	150 adults	Most Clear	Unclear	Clear	Unclear	Clear	Age-adjusted and sex -specific	Clear	34	0.67
Logroscino 2002	USA	Retrospective	110 adults ,35 children	Most Clear	Clear	Clear	Clear	Clear	Age- and sex-specific	No	28	1.0
Wu 2002	USA	Retrospective	12716 adults, 2885 children	Most Clear	Clear	No	No	Clear	Crude	No	19	0.78
ABSTRACTS												
Morton 2001	USA	Prospective	598 children	Most Clear	Clear	Clear	Unclear	Clear	Crude	Unclear	31	0.78
Towne 2002	USA	Prospective	318 adults	Most Clear	Clear	Clear	Unclear	Clear	Crude	Unclear	31	0.78
Trevathan 2002	USA	Retrospective	39,649 subjects	Most Clear	Clear	No	No	Clear	Age-specific	No	22	0.78

Table 2.3: Description, methodology scores and interrater agreement of methodology scores of population-based studies on the epidemiology of status epilepticus.

Methodology scores are based on the scoring system detailed in Table 2.1. *Methods definitions* refers to definitions outlined in the methodology of individual studies. *Inclusion criteria* refers to the criteria for selection of cases of SE from study population. *ILAE SE type* and *ILAE Aetiology* refers to whether the types of SE and aetiology of SE were classified according to ILAE guidelines. *Outcome* refers to whether the outcome parameters were clearly defined or not. *Standardization of Rates/Ratios* refers to whether rates/ratios were standardized and the type. *Ascertainment Adjustment* refers to whether an adjustment was made for degree of ascertainment. Maximum methodology score = 40, minimum score = 11. Displayed scores are that of the candidate.

2.4.2 Characteristics of SE

2.4.2.1 Incidence

The incidence of SE showed a bimodal distribution with peaks in children less than a year of age and the elderly (DeLorenzo et al., 1996; Hesdorffer et al., 1998; Wu et al., 2002). Children less than a year of age had the highest incidence (135-156/100,000/yr) (DeLorenzo et al., 1996; Hesdorffer et al., 1998). In general, males were more likely to have SE than females, and non-white patients were more likely to have SE than white patients. For further details, see Table 2.4.

2.4.2.2 Aetiology

The cause of SE varied according to age groups. In children, prolonged febrile seizures (35%) (Hesdorffer et al., 1998) and low anti-epileptic drug levels (21%) (DeLorenzo et al., 1996) were most common. In contrast, in adults, cerebrovascular disease/accidents, withdrawal or low levels (34%) of maintenance anti-epileptic drugs were most likely. Acute symptomatic SE accounted for most aetiologies across all age groups. Few episodes of SE were idiopathic (see Table 2.5 for further details on aetiology).

Incidence Rate (per/100,000 persons/year)	Richmond (Virginia, USA)	Rochester (Minnesota, USA)	Hessen (Germany)	French speaking Cantons (Switzerland)	California (USA)
Crude	41	-	15.8	9.9	6.8*
Ascertainment adjusted	61	-	17.1	-	-
Age-adjusted	-	18.3	17.1	10.3	-
In Children	38	24	-	21	3.86
In Adults	27	6	4	5	4.58
In the Elderly	86	62	54	15	14.6
Male : Female	-	2:1	2:1	2:1	1:1
Non-white : White	3:1	-	-	-	2:1
Peak age (years of age)	<1 , >60	<1 , >65	>60		<5, >60

Table 2.4: Incidence of SE according to research groups.

As the main aim of the St. Louis Group was to identify determinants of mortality associated with status epilepticus, the incidence of status epilepticus was not estimated in their study and consequently, the St. Louis Group is not listed in this table.
* Restricted to generalised convulsive status epilepticus.

Aetiology	Richmond			Rochester			Germany			Switzerland		
	C(%)	A(%)	T(%)	C(%)	A(%)	T(%)	C(%)	A(%)	T(%)	C(%)	A(%)	T(%)
Prolonged febrile seizures	-	-	-	23	0	8	-	-	-	-	-	-
Acute Symptomatic	57	72	70	46	52	50	-	-	87	66	61	63
Remote Symptomatic	38	25	27	18	20	20	-	-	63	25	31	28
Progressive Symptomatic	-	-	-	0	13	8	-	-	-			
Idiopathic/Unknown	5	3	3	13	15	14	-	-	9	9	8	9

Table 2.5: Aetiology of SE according to research groups. Californian Group excluded because proportional contributions of aetiologies from their study could not be determined.

C = Children A = Adults T = Total

2.4.2.3 SE and epilepsy

SE occurred within the context of epilepsy in less than 50% of cases overall. In children, 16-38% had a history of epilepsy, whilst in adults, 42-50% had a history of epilepsy (DeLorenzo et al., 1996; Knake et al., 2001). The percentage of SE patients with a history of epilepsy was higher in those who resided in rural areas (49-56%) compared to those who resided in urban areas (33%) (Coeytaux et al., 2001; Knake et al., 2001).

2.4.2.4 Duration

Most SE lasted less than 24 hours (DeLorenzo et al., 1996; Hesdorffer et al., 1998; Knake et al., 2001). All prolonged febrile seizures were shorter than 2 hours (Hesdorffer et al., 1998). In the paediatric population, the duration of continuous SE (median 60.5 minutes) was shorter than that of intermittent SE (median 87 minutes, $p<0.02$). In contrast, adults had no difference in duration of continuous SE (median 97.5 minutes) compared to intermittent SE (median 85 minutes) (Waterhouse et al. 1999).

2.4.2.5 Recurrence

Recurrence of SE occurred in 13.3- 18.5 % (DeLorenzo et al., 1996; Hesdorffer et al., 1998; Knake et al., 2001). A distinction between recurrence in adults and children was made in one study and in that study, recurrence was highest in the paediatric population (DeLorenzo et al., 1996). In adults, almost all (93.8%) patients with recurrences had a history of epilepsy (Knake et al., 2001).

2.4.2.6 Mortality

Mortality associated with SE across all age groups ranged from 7.6-22% during hospitalisation for SE or within 30 days of SE (short-term mortality) and 43% within 10 years following initial survival 30 days after SE (long term mortality). Age and aetiology of SE were the major determinants of short-term and long term mortality. Mortality is lowest in children (short term mortality from 3-9% and long term mortality around 7%) and highest in the elderly (short term mortality from 22-38% and long term mortality 82%). Amongst children, those aged under one year had the highest short term mortality (17-18%) (Morton et al., 2001). The Standardised Mortality Ratio (SMR), the relative risk of mortality compared to the general population, for subjects with long term mortality associated with SE was 2.8 (95% CI 2.1-3.5). The SMR in those older than 65 years was 2.2 (95% CI 1.6-2.9) and in those aged less 65 years, the SMR was 5.1 (95% CI 2.8-8.0).

Most deaths during hospitalisation for SE or within 30 days of SE occurred in those with an acute symptomatic aetiology (DeLorenzo et al., 1996; Logroscino et al., 1997). No deaths occurred in those with prolonged febrile seizures. In subjects with long term mortality, the SMR was significantly elevated in the acute and remote symptomatic SE groups. Acute symptomatic SE was associated with a higher mortality rate than idiopathic/cryptogenic SE. When mortality associated with different seizure types was reviewed, myoclonic SE in particular was associated with high short-term and long term mortality. Subjects with myoclonic SE had a significant relative risk (RR) of long term mortality in comparison to those with generalised SE (RR 4.0, 95% CI 1.3-13). There was no difference in short-term case

fatality between continuous and intermittent SE in children, but in adults, short-term case fatality was 31.4% in continuous compared to 19.6% in intermittent SE ($p<0.01$).

The effect of duration of SE and gender on short-term mortality is uncertain (Logroscino et al., 1997; Waterhouse et al. 1999; Wu et al., 2002) but there was increased long term mortality in subjects with SE lasting more than 24hrs when compared to those with SE lasting less than 2 hrs (RR 2.3, 95% CI 1.1-5.1) (Logroscino et al., 2002). Ethnicity had no effect on short-term mortality.

2.5 Discussion

The methodology for systematic reviews of non-interventional research is still in its infancy. In this systematic review of observational studies, the methodology has been based on recently published proposals for reporting meta-analyses of observational studies and guidelines for systematic reviews of qualitative studies (Abou-Khalil et al., 1993; Stroup et al., 2000). A similar methodology has been used in a published systematic review of incidence studies of epilepsy (Kotsopoulos et al., 2002).

Differences in definitions, classification of seizures and aetiologic criteria in epidemiological studies on epilepsy have often resulted in discordant results between studies and have made comparison of results difficult (International League Against Epilepsy 1993). In an attempt to address this issue, in 1993 the ILAE published guidelines for epidemiologic studies on epilepsy (International League Against Epilepsy 1993). Although the studies identified for the current systematic review were conducted after the ILAE's published guidelines for epidemiologic studies on epilepsy, there is still heterogeneity in the basic epidemiological parameters listed

above. Thus, a meta-analysis of the data from these studies was not possible but through the development of a unique scoring system based on a published proposal for reporting meta-analysis of observational studies (Stroup et al., 2000) and the ILAE's guidelines (International League Against Epilepsy 1993), the candidate was able to assess the methodological quality of studies and to compare studies. Most population-based studies on SE have high methodology scores. It is interesting that studies that had the largest study sample size (Trevathan et al., 2002; Wu et al., 2002) had the lowest methodology scores, suggesting that sample size alone is not an adequate guide to the quality of any individual study.

The range of reported crude incidence rates is wide (6.8-41/100,000/yr). The lowest incidence rate is from a study with a low methodology score (Wu et al., 2002). This suggests that the true incidence rate of SE is higher than the 6.8/100,000/yr in California. The remaining five studies that reported incidence rates had similar quality scores which were high (DeLorenzo et al., 1996; Hesdorffer et al., 1998; Knake et al., 2001) but despite this there was still a wide range of incidence rates (9.9-41/100,000/yr). It may be hypothesised that differences in case ascertainment between studies may partly explain the wide range of reported incidence rates. Quantification of ascertainment was not determined in the Swiss study (Coeytaux et al., 2001) and it is possible that their reported crude incidence of 9.9/100,000/yr may have been an underestimate due to incomplete ascertainment. The retrospective nature of the Rochester study suggests that their reported incidence of 18/100,000 persons/year may also be an underestimation. However, the Hessen and Rochester studies had similar ascertainment methodologies, similar degrees of ascertainment, similar quality scores, took underascertainment into account and reported ascertainment corrected

rates. Despite this, the reported ascertainment corrected incidence in the Richmond study is still treble that of the Hessen study (see Table 2.3 for further details). These results suggest that case ascertainment may not be the only explanation for the wide range in reported incidence.

Though the definition of SE was similar in all studies, inclusion criteria differed between studies. The Richmond, Rochester, Hessen and Swiss studies included convulsive (CSE) and non-convulsive SE (NCSE) while the Californian study excluded episodes of NCSE. NCSE only accounted for up to 6% of SE cases in studies that included both types of SE. The Swiss study, which has one of the lower reported rates, excluded patients with postanoxic encephalopathies which accounted for 10% of cases in the Rochester study. Therefore, difference in inclusion criteria may partially explain the diversity in incidence rates.

The Richmond group has partly attributed its much higher incidence to its greater non-white racial composition compared to other study areas and a higher incidence being reported in non-white subjects relative to white subjects. From the published literature and on discussion with two of the authors of the Richmond study, it remains unclear from the Richmond Group whether "initial" cases used to calculate incidence refer to cases with a lifetime first episode of SE, or first SE during the study period. If it is the latter, the reported incidence may be an over estimate and a more accurate incidence may be closer to that reported by the Rochester and Hessen Groups. It is also possible that the difference is partly explainable by a different age and or sex composition of Richmond compared to other study areas. Males are twice as likely as females to have an episode of SE. This gender difference may be partly due to a

higher incidence of certain aetiologies including cerebrovascular disease and brain trauma in males, but it may reflect a possible role of hormonal influences in the termination of seizures (Moshe et al., 1995; Standley et al., 1995).

In order to take into account differences in the composition of populations and to facilitate analysis of trends over time, standardized rates and ratios are important. This is reflected in the ILAE's guidelines for epidemiologic studies, which recommends that age- and sex-specific rates should be provided wherever possible and if summary frequency indices are reported, adjustment to a well-defined and accessible specified population should be made. Some studies in this systematic review do not report these standardized rates and is reflected in their quality scores (see Table 2.2).

Overall, the age adjusted incidence of SE in the white population in Europe and the USA is approximately 20/100,000/yr with higher incidence in early childhood and in the elderly. Epidemiological studies in countries with limited resources have found a higher incidence of epilepsy than developed countries but there are no such studies on status epilepticus. The effects of socioeconomic, cultural and environmental conditions on the incidence of SE are not known and studies examining these effects are needed in order to improve our understanding of SE worldwide.

Up to 50% of all incident episodes of SE occur within the context of epilepsy and less than half of these would have a history of epilepsy. Therefore, approximately 25% of patients with a life time first episode of status epilepticus have a history of epilepsy.

The Rochester Group reported a recurrence nearly one and a half times as great as in the Richmond and Hessen studies, but this difference is likely to be due to the follow-up period. In the former it was up to thirty years after incident SE compared to follow up of up to two years in the latter.

The onset of SE may not be observed and in the absence of continuous EEG monitoring there may be uncertainty about the cessation of seizure activity particularly when seizure control requires ventilatory support. Thus, determination of duration of seizures in observational studies is difficult and conclusions on the effect on seizure length on morbidity and mortality associated with SE should be interpreted with caution. It is important to note though, that there are experimental data in animals that suggest that longer duration of SE is associated with worse outcome (Meldrum et al. 1973). If longer duration of SE in man is associated with worse outcome, there is a potential danger of the continuation of SE without seizures detectable only by EEG as described by Treiman and colleagues (Treiman et al., 1987). In the Veterans Affairs study comparing four treatments for generalized CSE, 65% of patients with subtle SE died within 30 days of SE, compared to 27 % of patients with overt SE (Treiman et al., 1998). Therefore continuous EEG monitoring may be very important in guiding treatment of SE and reduce its associated morbidity and mortality.

Therapeutic regime may affect outcome by reducing seizure length. However, data on the treatment regime for SE in large population based studies were sparse. Two studies reported that a significant proportion of patients were not treated prior to arrival in hospital (Cascino et al., 2001; Coeytaux et al., 2001). This is important as

delayed treatment may increase the frequency of seizures lasting at least thirty minutes (Knudsen 1979). In their retrospective study, Cascino and colleagues also reported two other main observations on the treatment of SE. Patients who received an adequate initial dose of emergency anti-epileptic drugs (AEDs) were more likely to have seizure termination but patients were frequently given inadequate doses of emergency AEDs (Cascino et al., 2001; Coeytaux et al., 2001). The efficacy and safety of benzodiazepines in the treatment of SE in adults in the out of hospital setting has been demonstrated in a large randomized controlled study in adults (Alldredge et al., 2001). Other studies examining the treatment of SE, including the treatment in children, are needed for comparison, but the above data would suggest that early treatment with adequate doses of benzodiazepines in the out of hospital setting may be important.

It is possible that data from population-based studies on SE can provide information on the morbidity attributable to SE providing the research methodology is able to detect such downstream consequences. However, the problems of measuring attributable cognitive and behavioural problems are many and may be better addressed by studies of specific subgroups with specific syndromes within SE where the confounding factors can be minimised. Thus, morbidity attributable to SE was excluded from this review.

The data from this systematic review on the epidemiology of status epilepticus concur with those from hospital based studies in that age and aetiology are the most important determinants of short term case fatality in SE. Children have a low case fatality and acute symptomatic causes (excluding prolonged febrile seizures) are

associated with the worst prognosis (Aicardi et al., 1970; Aminoff et al. 1980; Dunn 1988; Yager et al., 1988; Maytal et al., 1989; Sung et al., 1989; Shorvon 1994b). The influence of duration of status epilepticus on short term case fatality is less clear. Two studies of similar methodological quality reported opposing findings (Logroscino et al., 1997; Waterhouse et al. 1999). The Richmond Group found that duration of status epilepticus was associated with increased mortality but the Rochester Group did not. However, the Richmond Groups' study (Waterhouse et al. 1999) was prospective and had a larger sample size and their findings are consistent with animal studies and clinical series that suggest that longer duration causes brain damage (Aicardi et al., 1970; Meldrum and Horton 1973; Dunn 1988; Yager et al., 1988; Sung et al., 1989; Hui et al., 2003).

Only one study has reported on long term mortality (Logroscino et al., 2002). The study was small and was conducted in a homogenous white middle class population thus limiting the generalisation of its findings. Like short term fatality, children fared better than adults and most deaths occurred in the elderly. However, the mortality in the elderly with SE is only increased two fold over that of general elderly population (SMR = 2). In those aged under 65 years, there is a five fold increase (SMR = 5). Together, these data suggest that SE is associated with increased mortality after initial survival but the increased risk of death associated with SE in the elderly is partly attributable to the higher death rate from any cause in the elderly. The long term standardised mortality ratio for symptomatic SE was significantly elevated, but not elevated in idiopathic or cryptogenic SE. This suggests that SE in isolation, without any identifiable underlying cause, does not alter long term mortality. Although this study group, the Rochester group, found that duration of SE had no effect on short

term mortality, they found that longer duration of SE was associated with increased long term mortality.

2.6 Conclusions

Although there are few population-based studies on status epilepticus, most are of good quality. The available data is consistent with the view that there are differences in incidence, aetiology and outcome between children and adults. SE is more common in children than adults (see Table 2.3), prolonged febrile seizures may account for up to a third of cases of SE in childhood (see Table 2.4) and mortality is lower in children. However, most studies eligible for this review were in primarily or exclusively adult populations and therefore paediatric results may not be an accurate reflection of the epidemiology of SE in the paediatric population. Of note, there are limited data within these studies on prolonged febrile seizures. Furthermore, data from adults may not be directly applicable to children as the physical and neurochemical characteristics of the developed brain differ to that of the developing brain (Holmes 1997). The results of the systematic review would also indicate that there is limited information on the association of ethnicity on SE and virtually none on the associations between socioeconomic, cultural and environmental differences and SE. The data from the systematic review also suggest that longer duration of SE is associated with increased short term and long term mortality. There are sparse data on the treatment of SE in the general population but the available data indicate that a significant proportion of patients are not treated or inadequately treated in the prehospital setting. Therefore, in order to ultimately improve the management of children with CSE, there is an urgent need for population-based studies on CSE in a

purely paediatric population to more accurately assess the frequency, morbidity and mortality of CSE and to identify factors, including the role of prehospital treatment of CSE, that may influence these variables.

Therefore the aims of the studies to be reported in this thesis are:

1. To estimate the incidence, occurrence, aetiology, seizure characteristics, recurrence and the short term mortality associated with childhood CSE

2. To investigate the relationships between ethnicity, socioeconomic status, age and incidence of childhood CSE

3. To identify factors associated with CSE lasting longer than 60 minutes compared to CSE lasting 30-60 minutes

4. To characterise the emergency treatment of childhood CSE in the study population

5. To characterise the clinical features of children admitted to PICU for CSE and identify factors associated with admission to PICU for CSE

CHAPTER 3: CENSUS 2001 AND NORTH LONDON

3.1 Introduction

To address the aims of this study, accurate population data and a suitable well-defined childhood population are required. As the most comprehensive, accurate source of available information about the general population in the United Kingdom (UK) is obtained from the Census and this study was conducted over the period 2002-2004, accurate population based data for this study were obtained from Census 2001.

In order to identify all possible cases of CSE within a specified geographical area, a network of hospitals, ideally with a well established referral system serving that area, needs to be identified. To assess the effect of socioeconomic status and ethnicity on the incidence of CSE, a geographically defined population of varied ethnic and socioeconomic composition is required. The current study was carried out in North London where there are more than half a million children and there is a wide cross-section of ethnic and socioeconomic groups. North London has a well established referral network between hospitals with paediatric services and has a designated children's acute transport service (CATS) to assist in the management of critically ill children before and during transfer to a paediatric intensive care unit.

In this chapter, Census 2001 (including a scoring system for assessing socioeconomic profile of local areas) and North London (including the referral network between hospitals as well as the age, ethnic and socioeconomic profile of North London) are described.

3.2 Census 2001

3.2.1 Background

Each decade in the United Kingdom, a day is set aside for a Census - a count of all people and households. In England and Wales, the Census is planned and carried out by the Office for National Statistics and elsewhere in the UK, responsibility lies with the General Register Office for Scotland and the Northern Ireland Statistics and Research Agency. The latest Census was held on April 29, 2001.

Every effort was made to include everyone in the Census. It was designed to cover the entire population at the same time and to ask the same core questions everywhere, thus facilitating comparisons between different parts of the country. Data provided by the Census include an accurate count of the population in each area as well as accurate data on the age, ethnic and socioeconomic make up of the population. Such information assists Government in determining the size of grants allocated to each local authority and health authority. In turn, these authorities use the census data to allocate resources and plan programmes and services.

3.2.2 Census 2001 Methods

For the Census 2001, a major publicity campaign was undertaken to heighten awareness that a Census was being taken. A special programme was established to help groups who might have had difficulty with completing the Census forms e.g. the visually impaired and those who were unable to read or write English. Using a field force set up throughout the country, Census forms were delivered to every household. Completed forms were either posted back to temporary local offices or collected by

the field force. There was a legal obligation on every household to complete a Census form.

Questions from the form provided information on accommodation, family relationships, demographic characteristics, migration, cultural characteristics, health and provision of care, qualifications, employment, workplace and journey to work. The 2001 Census forms were scanned and the answers coded into categories by either automatic systems that recognised terms given in response to questions or by manual coding. It has been previously shown that the database is well validated (Office of National Statistics 2001). In order to safeguard confidentiality, the Census forms were collected and processed in secure conditions. Statistical results of the Census are presented in a manner to protect against the inadvertent disclosure of information about identifiable individuals.

Data from UK Censuses are collated to provide statistics such as age-specific population and ethnic, socioeconomic and gender composition of small local areas within the UK. Such statistics, Small Area Statistics (SAS), were aggregated and presented for Enumeration Districts (EDs) as the smallest output geographical area for all UK Censuses from 1961 to 1991. SAS for larger areas such as local authorities, wards and districts could be compiled by combining the results from EDs. However the size and character of each ED were variable, making the resultant SAS less than ideal for statistical analysis and comparison of geographical area. An alternative to EDs as the smallest geographical output area for SAS was needed.

For Census 2001, SAS are determined from Super Output Areas (SOA) rather than EDs as the smallest output geographical area. SOAs are areas grouped together using zone design software creating statistical areas that are similar in size (average of 1,500 residents and 400 households) and social homogeneity. Each area is usually comprised of whole unit postcodes and is regularly shaped with 'natural' boundaries where possible. Therefore, SAS indicators from Census 2001 reflect an up to date profile of the local area. One such indicator is the Indices of Multiple Deprivation 2004 (IMD 2004), which were primarily determined from data from Census 2001 supplemented by local data.

3.2.3 Indices of Multiple Deprivation 2004 (IMD 2004)

The aim of creating indices to measure deprivation at the local level, in order to identify priority areas and to target programmes, has been a consistent feature of government policy since at least the mid 1960s. These indices have traditionally been concerned with a single specific area of policy such as health but deprivation is multi-dimensional rather than uni-dimensional. Thus, since the 1980s, the creation of a national index of "multiple deprivation" at the local level has become a central government issue. Such indices of multiple deprivation that have been developed have included the Carstairs Index, Townsend Material Deprivation Index, Jarman Underprivileged Area Index, Indices of Multiple Deprivation 2000 and the more recent Index of Multiple Deprivation 2004 (Carstairs and Morris 1989; Morris and Carstairs 1991; Department of the Environment 2000; Office of the Deputy Prime Minister 2004).

IMD 2004 is a unified, multiple deprivation, SOA based index, that estimates social as well as economic deprivation. It is an improvement on its predecessors as it incorporates more recent data and more aspects of deprivation. IMD 2004 was constructed by the Social Disadvantage Research Centre (SDRC) at the Department of Social Policy and Social Research at the University of Oxford. It is based on the concept that there are distinct dimensions of deprivation that can be identified and estimated separately. It is comprised of seven separate dimensions of deprivation, each with its own measured indicators of deprivation, whose scores have been standardised and combined in a weighted manner to make a single score (see Appendix 2 for further details). IMD 2004 is based on 37 indicators in total. Thus, each local area, SOA, has seven separate scores for seven different areas of possible deprivation: Income, Employment, Health and disability, Education, skills and training, Housing and Services, Crime and Living Environment. Each local area can be ranked in relation to all other local areas in the United Kingdom according to any of the dimensions of deprivation or the combined IMD 2004 (Office of the Deputy Prime Minister 2004).

There are 32,482 SOAs throughout the United Kingdom with associated IMD 2004 scores. IMD 2004 scores range from 0.55 to 85.69, with higher scores correlating with a higher degree of socioeconomic deprivation.

In North London, there are 2,007 SOAs with IMD 2004 scores ranging from 2.36 to 76.36. By determining the full postal code of the home address of an individual, the corresponding SOA and IMD 2004 score may be determined. As individuals within an area all experience the various aspects of deprivation within the area, IMD 2004

scores may be used as a proxy measure of an individual's extent of socioeconomic deprivation.

3.3 North London

3.3.1 Geography

For the purposes of this study, North London is defined as a 494.29 square kilometres region of London north of the River Thames constituted by the fifteen boroughs of Barnet, Brent, Camden, City of London, Enfield, Hackney, Hammersmith and Fulham, Haringey, Harrow, Islington, Kensington and Chelsea, Newham, Tower Hamlets, City of Westminster and Waltham Forest (see Figure 3.1).

Figure 3.1: Area bounded by ——— represents North London.
- Accident and Emergency (A&E) departments
- PICUs

3.3.2 Acute emergency services for children in North London

3.3.2.1 Hospitals with 24 hr A&E services

In North London, accident and emergency services are provided through the National Health Service (NHS). Patients that are taken to the accident and emergency

department (A&E) by ambulance are taken to their nearest A&E by road. Most patients will be transported to a hospital within their borough, but occasionally, their nearest hospital will be in an adjacent borough. Mapping the network of hospitals in London that provide 24-hour A&E services for children against the geographical boundaries of North London, shows that there are seventeen hospitals that may provide 24-hour A&E services for children normally resident in North London (see Figure 3.1). These hospitals are: Barnet General Hospital, Central Middlesex Hospital, Chase Farm Hospital, Chelsea & Westminster Hospital, Homerton Hospital, King George Hospital, Newham General Hospital, North Middlesex Hospital, Northwick Park Hospital, Royal Free Hospital, Royal London Hospital, St. Mary's Hospital, St. Thomas' Hospital, University College London Hospital, Watford General Hospital, Whipp's Cross Hospital and the Whittington Hospital. Any study on a North London population that involves a condition in which emergency treatment is urgently needed, such as CSE, requires that all these hospitals are included.

3.3.3.2 Paediatric Intensive Care Units and Children's Acute Transport Service

To facilitate the fast, effective and efficient transfer of critically ill children to a Paediatric Intensive Care Unit (PICU), a designated Children's Acute Transport Service (CATS) has been established in North London. Children requiring intensive care are referred directly to CATS, where telephone consultation with paediatric intensivists and liaison with other sub-specialists are also provided. Most critically ill children within North London are treated in two PICUs based in North London: Great Ormond Street Hospital PICU and St. Mary's Hospital PICU, but occasionally, children are treated at one of the three PICUs based in South London: Guy's Hospital

PICU, King's College Hospital PICU and St. George's Hospital PICU (see Figure 3.1). Therefore, any study in North London involving a condition that results in critically ill children, such as CSE, requires the inclusion of all these PICUs as well as CATS.

3.3.3 Population data on North London

From Census 2001, the total population of North London is 3,022,519. Of these, 605,320 (20%) are children (aged less than 16 years of age). Within North London, England and Wales approximately 20% of the population are children. There are similar proportions of men and women in North London, England and Wales but there is a difference in the ethnic composition. Within North London, people of white ethnicity account for 67% of the population compared to 92% throughout England and Wales. For further details of the ethnic, sex and age composition of England and Wales and North London, see Appendix 3. In the childhood population, the borough of Hackney is the most densely populated borough within North London (2489 children/km^2) and the City of London is the least dense (232/ km^2). For further details on population density of boroughs in North London see Table 3.1.

3.3.3.1 Ethnicity composition of North London

North London is cosmopolitan. Half of children are of white ethnicity. There are similar proportions of children of Asian and black ethnicity and almost ten percent of children are of mixed ethnicity. Children of any other ethnic group account for three percent of the childhood population. For further details on the ethnic profile of North London see Appendix 3.

3.3.3.2 Socioeconomic composition of North London

There are varying levels of socioeconomic deprivation in North London. Within boroughs there are very deprived areas intermixed with those with little deprivation. IMD scores range from 2.36 to 76.36 with higher scores associated with increasing socioeconomic deprivation. The mean IMD 2004 score of the fifteen boroughs of North London range from 13.57 in Harrow to 45.75 in Tower Hamlets. For further details on mean IMD scores of boroughs of North London, see Table 3.1.

Boroughs	Childhood Population	Childhood Population Density (number per sq km)	Mean IMD 2004
Barnet	63756	735	16.09
Brent	52169	1207	25.93
Camden	32867	1508	34.65
City of London	673	232	15.32
Enfield	57793	715	23.11
Hackney	47430	2489	45.05
Hammersmith & Fulham	27226	1660	27.79
Haringey	44605	1507	37.69
Harrow	41691	826	13.57
Islington	32242	2170	42.66
Kensington and Chelsea	24795	2044	21.65
Newham	63841	1763	40.53
Tower Hamlets	44890	2271	45.75
Waltham Forest	46868	1208	30.25
Westminster	24474	1139	31.66

Table 3.1: Childhood population density and mean IMD 2004 for boroughs of North London (Office of National Statistics 2004; Office of National Statistics 2004).

The contents of this chapter illustrate that North London has a large paediatric population with varied ethnic and socioeconomic composition within a well defined geographical area and a well established referral network for paediatric clinical services. Thus, it is feasible to conduct a prospective paediatric population based study on CSE in North London but the success of such a study is reliant on the degree of ascertainment of cases.

In the next chapter, the methods used to identify all possible cases of childhood CSE in North London during the study period and the statistical method used to estimate degree of ascertainment will be described.

CHAPTER 4: METHODS FOR ASCERTAINMENT AND CAPTURE-RECAPTURE

4.1 Introduction

One of the main strengths of population based studies is that in principle, they are free from the referral bias which may occur in hospital based studies. The higher the degree of case ascertainment the greater the likelihood that results may be more applicable to the general population. Therefore, for a population based study on CSE in childhood, as many cases of childhood CSE as possible need to be identified; ideally, all should be identified. Identification of cases using a single source is likely to result in an underestimation of the total number of cases. Therefore in this study, the candidate used a multi-source identification system involving paediatricians from the network of hospitals described in the previous chapter. Cases were identified primarily through a passive telephone notification system directed at trainee paediatricians, nurses and administrative staff, an active regional surveillance scheme, based on the British Paediatric Surveillance Unit's methodology and directed at consultant paediatricians and audits of paediatric admissions to hospitals in the North London network and referrals to the Children's Acute Transport Service. Notifications of cases by the regional surveillance scheme and telephone notifications system were administrated by a centrally based coordinating centre.

To facilitate the identification of cases of CSE and subsequent data collection on such cases, the candidate co-founded a research collaborative group constituted by the principal researchers and a paediatrician from each hospital within the network previously described. The main initial remits of the research collaborative group were

to publicise the study in their local hospital, assist in the design of the data collection methodology and to aid data collection. A steering group of experts in paediatric epidemiology and biostatistics and paediatric neurosciences was established by the candidate to oversee the study. Members of the Steering Group were Dr. Rod Scott and Professor Brian Neville from Paediatric Neurosciences, Dr. Helen Bedford, Dr. Angie Wade and Dr. Pat Tookey from the Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, London and Mr. Richard Lynn from the British Paediatric Surveillance Unit (BPSU).

It is recognised that the lists of patients identified from either of these sources could be incomplete and consequently a method of estimating the degree of ascertainment of cases was required. Capture-recapture is such a method. The systems of identification of cases of CSE for this study and the application of capture-recapture to the data obtained through those systems are reported in this chapter.

4.2 A telephone notification system

As convulsive status epilepticus is an acute neurological emergency, the candidate wanted to identify all patients with convulsive status epilepticus as soon as possible after presentation to hospital to maximise the accuracy and completeness of data collection. Therefore, the primary source of identification of children with CSE used in the current study was a telephone notification system. Children with CSE identified through telephone notifications were defined as being identified by "PHONE".

4.2.1 Design of the telephone notification system

The candidate established a designated 24 hour telephone notification hotline at the research coordinating centre. The hotline was manned by a research administrator from 9:00 am to 5:00pm weekdays and outside of those hours, an answering service was in place. A telephone number that could be readily remembered in an alphanumeric form and associated with the study was specifically chosen i.e. 02072783777, alphanumeric form 020-72STEPSS. Through an intensive schedule of regular promotional talks by the candidate at hospitals within the research network and to CATS, plus the distribution of promotional "post- its", posters and wallet sized laminated cards to medical and nursing staff at hospitals within the network and from CATS, trainee paediatricians, nursing and administrative staff were asked to report cases of CSE immediately after presentation to the research coordinating centre. To further maximise trainee paediatricians' awareness about the study, local collaborators included information on the study as part of the induction process for each doctor that joined the paediatric staff.

4.2.2 Potential weaknesses of the telephone notification system

The main potential weakness of this telephone reporting system is that it was passive. Hence the need for the publicity and motivational efforts described above. An additional alternative, active source of notification of cases of notification, such as that conducted by the British Paediatric Surveillance Unit (BPSU), was required.

4.3 BPSU-like regional surveillance scheme

The next source of identification of cases considered was modelled on the system of the British Paediatric Surveillance Unit (BPSU) of the Royal College of Paediatrics and Child Health (RCPCH) as it's effectiveness in assembling sufficient cases of particular conditions to study epidemiological characteristics has been researched and recognised (Verity and Preece 2002). Cases identified through the BPSU-like scheme were defined as being identified by "FORMS".

4.3.1 BPSU methodology

The BPSU conducts a national active surveillance system based on a postal questionnaire scheme. At the end of each month the BPSU mails out a report card containing a list of conditions being surveyed to every senior doctor who is likely to have clinical responsibility for children with rare conditions. Reporting clinicians are asked to check boxes against any of the reportable conditions they have seen in the preceding month, or to check a "nil return" box if none have been seen and return the card to the BPSU. "Positive" returns are notified to the appropriate investigator, who contacts the reporting clinician directly for data collection. Supplemental data are provided through other data sources such as laboratory reports via the Health Protection Agency (HPA), Hospital Episode Statistics. The BPSU **does not** receive any patient identifiable data and is not involved with direct patient contact. Investigators that need to contact families directly do so through doctors caring for those families.

4.3.2 Main weakness of BPSU

The main concern about the BPSU scheme is its completeness of the ascertainment of cases. At the end of each month, responders are asked to report cases in the preceding month. Thus, there may be an element of recall bias with subsequent missed cases. Though the BPSU has a 92% response rate, its ascertainment of eligible cases has been estimated at 45% (Rahi and Dezateux 1999).

4.3.3. A regional BPSU-like scheme rather than the national BPSU scheme

Generally, only rare childhood illness or diseases that require ascertainment of cases on a national scale in order to generate sufficient numbers for study are included in the BPSU scheme. CSE is not uncommon and the current study was regional rather than national. In addition, the BPSU does not receive any patient identifiable information and such information was required in the current study to confirm residence within North London, to prevent multiple counts of single cases and to identify recurrences of episodes of CSE. Therefore, after discussion with the BPSU, the candidate's population based study on childhood CSE in North London was not considered suitable for the BPSU. Nonetheless, the BPSU, along with the Centre for Paediatric Epidemiology and Biostatistics of the Institute of Child Health, assisted in the design and implementation of a regional active surveillance scheme for the study.

4.3.4 Design of regional BPSU-like scheme

Any such surveillance scheme should aim to also have a high response rate and ideally, a better ascertainment than the BPSU. In a systematic review of strategies for increasing response rates to postal questionnaires, Edwards and colleagues (Edwards et al., 2002) examined 292 eligible trials including a total of 258, 315 participants that

evaluated 75 different strategies for increasing response to postal questionnaires. They identified a range of strategies that seem to increase response to postal questionnaires including shorter questionnaires, the use of brown envelopes versus white envelopes, first class outward mailing versus other classes and postal follow up including a questionnaire versus postal follow up excluding a questionnaire. For further details on the effect of strategies on improving response rates, see Appendix 4.

Bearing the results of Edwards systematic review in mind, monthly surveillance forms used in the regional BPSU-like scheme were short (single side of A4 paper), coloured, personalised, forms that were sent first class in brown envelopes with enclosed self addressed return envelopes. Paediatricians were asked to indicate how many cases of CSE they had seen in the preceding month and to provide details on patient initials, date of birth and date of the CSE event (Appendix 5). If there was no response, paediatricians were sent a follow-up note with another copy of the surveillance forms (see Appendix 6).

A comprehensive mailing list of paediatricians was compiled by contacting all paediatric departments within the research network and requesting the names of all consultant paediatricians, regardless of subspecialty. In order to maximise completeness, the list, which was updated yearly, was cross-referenced by the BPSU against its list of paediatricians in London. Prior to commencement of the surveillance scheme, each month for 2 months, information sheets and letters were sent to each paediatrician in the network informing them of the study and the surveillance scheme and requesting their assistance in the study (Appendix 7 and

Appendix 8). Within the first 3 months of commencement, the BPSU included information on the study in its quarterly newsletter to all paediatricians.

4.3.5 Potential weaknesses of the regional BPSU-like scheme

Like the BPSU, the main potential weaknesses of this regional surveillance scheme are underascertainment and delayed identification of cases.

4.4 Audits of admissions to hospitals and referrals to PICU

This third source of identification of cases was based on a search for specific International Classification of Diseases (ICD) codes amongst hospital admissions and/or referral diagnoses to CATS. Cases identified through the audits were defined as being identified by "AUDIT". The ability to exchange comparable data from one geographical location to another, nationally and internationally, to allow comparison from one population to another and to permit longitudinal study of diseases, is one of the major strengths of the ICD.

4.4.1 International Classification of Diseases

The International Classification of Diseases (ICD) has been customarily revised every 10 years in order to keep up with the advances of medicine and is currently in its tenth revision (ICD-10). The ICD functions as a classification system of causes of morbidity and mortality as well as basis for medical record indexing and retrieval. Through an alphanumeric coding scheme, diagnoses are coded using a core classification from which a series of subcategories can be derived, each reaching a different degree of specificity and adapted to a particular specialty or type of user.

The coding scheme is complex and for accurate coding, people who code diagnoses should be trained appropriately in its usage.

4.4.2 Potential weaknesses of identifying cases of CSE using ICD codes

The accuracy of data obtained through ICD codes is limited by the precision of the coding process which is prone to errors (MacIntyre et al., 1997; Fabry et al., 2003; Rinaldi et al., 2003). Clinicians should accept personal responsibility for coding patients' diagnoses at the time of consultation or discharge from hospital (Wood et al., 1989) but the workload of clinicians frequently limits the time available to learn how to code and to code diagnoses. Uncertainty of diagnosis can be common, particularly in patients with complex problems (MacIntyre et al., 1997). Coding is usually performed manually and attempts to develop computerized tools to increase the efficiency and accuracy of coding using ICD 10 have proven difficult (Fabry et al., 2003). Therefore, coding remains primarily a manual task conducted retrospectively by non-clinicians not directly involved in patient management and with varying degrees of training in coding. On this basis, epidemiological data and forecasts for allocation of health resources based only on the ICD system must be considered with caution.

4.4.3 Conduct of audits of hospital admissions and referrals to CATS

Each year, a complete review of all cases of SE and febrile seizures was performed. The review evaluated all hospital ICD-10 codes for SE (G41) and febrile seizures (R56.0) and referrals to CATS for seizures/convulsions/status epilepticus. The labour intensive nature of these yearly reviews made it impossible for the candidate to conduct them in the twenty one hospitals within the research network. Over the two

year study period, reviews were conducted at Great Ormond Street Hospital, a tertiary hospital with a PICU but without an A&E department, at the CATS centre and six randomly selected North London hospitals with 24 hour accident and emergency services. Random selection of the six North London hospitals was conducted using SPSS version 10 (Chicago, Illinois). All North London hospitals were listed by the candidate on an SPSS version 10 (Chicago, Illinois) datasheet and a fellow PhD student used the software to randomly select six hospitals from the datasheet. As there was a delay in the identification of cases of CSE through the audits, in order to minimise bias, the clinical details of episodes of CSE identified only through these audits were not included in this study. The number of cases identified by audits whether in isolation or also by the other two systems described above were recorded in order to assess the degree of ascertainment through capture-recapture (see section 4.6 below for details on capture-recapture).

4.5 Identification of cases of CSE through other sources

As the candidate was based at Great Ormond Street Hospital for Children NHS Trust (GOSH), some cases of CSE were reported directly to the candidate by intensive care and neurology staff. Occasionally, cases were also reported by electronic mail. As these were all passive notifications immediately after admission, such cases were considered "telephone notifications" and were defined as being identified by "PHONE".

4.6 Capture-recapture

4.6.1 Introduction

As the name suggests, capture – recapture methods were originally developed for use in animal ecology, from which they draw their name (Shepherd 1994) and were later adapted for use in connection with human populations. Capture-recapture methods in epidemiology are attempts to estimate or adjust for the extent of incomplete ascertainment using information from overlapping lists of cases from distinct sources. The number of cases identified by each source and the overlap between sources are used to estimate the total number of cases in a population and by extrapolation, the number of unascertained cases. Different capture-recapture models are used according to the number of sources of identification and the different models are described in Sections 4.6.3 and 4.6.5. The value of capture-recapture has been demonstrated even for apparently exhaustive studies. In a study of the prevalence of Huntington's disease in Maryland on April 1, 1980, the authors used 14 different ascertainment sources, including genealogical records from pedigrees, in an attempt to identify all possible cases and reported a total of 217 cases on the prevalence day (Folstein et al., 1987). By applying capture-recapture methodology, Hook and Regal demonstrated that the ascertainment from that apparently exhaustive study was between 59 to 76%, suggesting that the true estimate was higher than that reported (Hook and Regal 1992).

4.6.2 History of adaptation for human population studies

According to Seber, the first use of the capture-recapture method can be traced to Laplace who applied it to estimate the population of France in 1786 (Seber 1982). The first application of the method to human health may be regarded as Sekar and

Deming's use of the method to estimate birth and death rates and the extent of registration in the United States of America in 1949 (Sekar and Deming 1949). Since then a number of epidemiological studies have successfully used the method (Tracey 1941; Shapiro 1949; Wittes and Sidel 1968; Wittes et al., 1974; Hogan 1993; Rahi and Dezateux 1999; Whitfield and Kelly 2002; Acin et al., 2003; Gill et al., 2003; Pezzotti et al., 2003). The earliest epidemiological studies using the method were conducted in 1968 by Wittes and Seidel who estimated the frequency of birth defects (Wittes and Sidel 1968) and by Lewis and Hassanein who investigated hospital infections in 1969 (Lewis and Hassanein 1969). However, the method was not taken up and it was not until the late 1980s that the method began to be used to any great extent. The early papers almost exclusively used the two sample approach but recently, new methodologies using multiple samples have been developed (Brodie 1990; Derroch et al., 1993; Chao et al., 2001;).

4.6.3 Two-sample capture-recapture model

4.6.3.1 Application to ecology studies

The simplest capture-recapture model is the so-called two sample model, also called the Petersen method because of Petersen's work with tagged fish in1894 (Hook and Regal 1995) and is used solely to estimate the unknown size of a population. An animal experiment will be used illustrate the method. Assume that a first sample of animals (n_1) is captured, marked and returned to the total population of animals (N). Then the marked proportion in the population is n_1 / N. A second sample of animals (n_2) is captured and this includes a number (m_2) that were previously marked. Given that the two samples are independently drawn, one would expect the proportion of marked to unmarked animals in the second sample to be the same as the proportion of

the number of animals captured in the first sample to the number in the whole population i.e. $m_2/n_2 = n_1/N$, and therefore $N = n_1n_2/m_2$ (Wittes and Sidel 1968; Hook and Regal 1995).

Confidence intervals for the ascertainment-adjusted estimate of N may be calculated using the formula: 95% confidence intervals = $N \pm 1.96[\sqrt{[(a+b+1)(a+c+1)(b)(c)]} / [(a+1)^2 (a+2)]$, where a is the number of animals identified in both samples, b is the number of animals identified only from the first sample and c is the number of animals identified only from the second sample (Regal and Hook 1984).

4.6.3.2 Application to human population studies

The capture-recapture method can, in principle, be applied to any human population studies in which there are two incomplete lists i.e. one replaces "being caught in sample x" with "being on list x" and referring to the method as "two *source* capture-recapture" instead of two *sample* capture-recapture" . This is the case in epidemiological studies where lists may be collated from various sources such as hospital records, laboratory records, clinic records and others. However, not all cases may be admitted to hospital, or have laboratory investigations or be seen in clinic. Thus, lists collated from such sources may be incomplete and the challenge is to estimate those cases that are missing from both lists. Intuitively, the two source method may appear simple and straightforward but in order for capture-recapture estimates to be valid, four key assumptions should be fulfilled.

4.6.3.3 Assumptions for capture-recapture methods

1. There is no change to the population during the investigation (the population is closed).
2. There is no loss of the tag/identifier (individuals can be matched from capture to recapture).
3. For each source, each individual has the same chance of being included in the sample (equal catchability)
4. The sources are independent.

In the current study, assumptions 1 to 3 were fulfilled i.e. the North London population size was approximately constant during the study period; unique patient identifiers collected on each patient in this study including patient initials, gender, date of birth, home postal code, hospital registration number and admitting and or referring hospital ensured that individuals could be matched across all sources of identification of cases of CSE; a strict definition of CSE was used to prevent different interpretations amongst clinicians. It is, however, unlikely that assumption 4 was fulfilled in this study. Generally, independence between sources is untenable in practice in epidemiological studies and this is the main weakness of a two-source capture-recapture model (Brenner 1995).

4.6.4 Dependence between sources in capture-recapture

There are two types of dependence (Chao et al., 2001):

1. Local dependence (list dependence, local list dependence) within each individual. The inclusion of an individual in one source has a direct causal effect on their inclusion in other sources. For example, the probability of an individual attending

a sickle cell disease clinic for treatment depends on the results of his blood tests for sickle cell disease. Consequently, ascertainment of cases from a sickle cell disease clinic and from sickle cell disease blood tests become dependent. In the current study, local dependence is likely to be low or absent as the identification of a child with CSE by the BPSU-like system, the telephone reporting system, or the audits of hospital admissions does not have a direct causal effect on inclusion in any of the others.

2. Heterogeneity between individuals. The ascertainment of sources may become dependent if the probability for capture is heterogeneous among individuals. For example, more severe cases are more likely to be reported by various sources than less severe cases and between subgroups of the population, there is varying access to medical care and hence varying likelihood of eventual diagnosis and registration. It is possible that such dependence exists in this study but to what extent is uncertain.

Lack of independence between sources leads to a bias in estimated rates. It is not possible to quantify dependence in the two-sample method and though most studies resolve this problem by simply ignoring any possible dependence, the practice is not ideal (Chao 1987; Chao et al., 2001). As a result, several models, applicable to *k*-sources, where *k* is at least three, incorporating dependence among samples have been proposed in the literature.

4.6.5 Three or more sources model

These include ecological models, log-linear models (Agresti 1994; Coull and Agresti 1999) and the sample coverage approach (Chao and Tsay 1998; Tsay and Chao 2001). For the purposes of this thesis, only the latter two models are used as they are mainly useful for two to five sources of data and are hence more applicable to epidemiological studies.

4.6.5.1 Log-linear Models

In log-linear models, data are considered as a form of an incomplete 2^k contingency table (k is the number of lists) for which the cell corresponding to those individuals not listed by all samples is missing. A series of possible interactions between lists is modelled with resultant plausible corresponding estimates for each. How well the model fits the data is assessed using the deviance statistic, with the best models corresponding to those with the smallest deviance statistic (Chao et al., 2001). However, equally fitting models may give quite different estimates (Coull and Agresti 1999) and as the number of lists increases, the number of adequate models and thus, model selection becomes more difficult (Hook and Regal 1995). Therefore, an alternative approach may be required.

4.6.5.2 Sample Coverage Approach

The sample coverage approach provides such an alternative model. The approach was originally proposed by Good and Turing (Good 1953) and has played a major role in the classical species estimation for heterogeneous populations. Fundamentally, the concept is that a good estimate of the sample coverage may be made even in the presence of two types of dependencies i.e. local dependence and or heterogeneity

between individuals. Thus, an estimate of the population size can be derived through the relationship between population size and sample coverage. Three estimates are calculated corresponding to low sample coverage, high sample coverage and complete sample coverage (complete independence between lists) with the best model for the data corresponding to that with the smallest deviance statistic (Chao et al., 2001).

Therefore, by applying both log-linear modelling and sample coverage approach, a series of possible estimates of population size, along with their deviant statistics may be determined. Amongst best fit models, that which has the lowest (highest) estimate is considered the best estimate of the lower (upper) limit of the true size of the population. CARE -1, a program developed by Chao and Tsay (Chao et al., 2001) and capable of applying the Log-linear model and the Sample coverage approach was used for NLSTEPSS.

4.6.6 Number of sources required for capture-recapture

In epidemiological studies different ascertainment methods are usually used and therefore, as the number of sources increases, dependence measures increase. Increasing the number of sources often costs more and requires additional effort, but does not necessarily produce better results, particularly when different ascertainment methods are used (Offringa et al. 1991). Only three or four sources are recommended unless similar methods of ascertainment are applied (Chao et al., 2001).

4.6.7 Application of capture-recapture to NLSTEPSS

Three sources of identification of cases were used in this study i.e. "PHONE", "FORMS" and "AUDITS" but audits were only conducted at a random sample of

hospitals in the research network and at CATS. As independence between sources is not guaranteed in two source models and dependency can be accounted for in three source models, the candidate applied a three source capture-recapture model to the data. Using both log-linear and sample coverage approaches, estimates of the lower and the upper limit of the number of missed cases of CSE and degree of ascertainment in the random sample of three sources were initially calculated and the results were extrapolated to the data obtained from the two lists covering the entire research network . Consequently, in the current study, ascertainment- adjusted rates are presented as a range with an estimated lower limit and upper limit and a corresponding 95% confidence interval.

The previous sections of this chapter illustrate that through a multi-tiered notification system, exhaustive efforts were made to identify as many cases of childhood CSE as possible within North London during the study period. Despite these efforts, the candidate recognised the possibility of unascertained cases but by utilising capture-recapture methods, an estimate of the number of missed cases could be determined and ascertainment adjusted estimates of the incidence and occurrence of CSE could hence be calculated.

PART TWO

A PROSPECTIVE POPULATION BASED STUDY OF CONVULSIVE STATUS EPILEPTICUS IN CHILDHOOD

CHAPTER 5: INCIDENCE, AETIOLOGY, SEIZURE CHARACTERISTICS AND OUTCOME OF CONVULSIVE STATUS EPILEPTICUS IN CHILDHOOD IN NORTH LONDON

5.1 Introduction

In Chapters 1-4, the need for a paediatric population based study on status epilepticus, the feasibility of conducting such a study in North London and the methods for identification of cases and assessment of ascertainment were outlined. Status epilepticus may be convulsive or non-convulsive in nature and whilst convulsive status epilepticus is a clinical diagnosis, non-convulsive status epilepticus is an EEG diagnosis (Kaplan 1999; Drislane 2000; Husain et al., 2003; Ruegg and Dichter 2003). Therefore, as immediate EEG investigation is not universally available for children admitted to hospitals in North London, NLSTEPSS was restricted to episodes of convulsive status epilepticus (CSE).

From the systematic review of population-based studies on SE reported in Chapter 2, the incidence of status epilepticus in children is higher in the younger age groups, particularly in those aged less than one. There is also some evidence that the incidence of status epilepticus may be higher in non-white ethnic groups compared to white ethnic groups, raising the possibility that there may be innate or genetically determined biologic mechanisms for this increased incidence. A growing body of research suggests, however, that ethnicity has strong social dimensions that influence health. Demonstrated racial/ethnic "effects" may be intricately related to socioeconomic factors, because race/ethnicity interacts with and is confounded by

social class or socioeconomic status and therefore studies on the effect of race/ethnicity on disease may be strengthened by the inclusion of socioeconomic factors. Within the published literature, there are no data on the independent effects of ethnicity and socioeconomic state on the incidence of status epilepticus.

There is evidence from animal and human studies that suggest that the morbidity and mortality associated with status epilepticus increases with increasing seizure duration (Aicardi et al., 1970; Meldrum et al. 1973; Dunn 1988; Yager et al., 1988; Logroscino et al., 1997; Logroscino et al., 2002; Hui et al., 2003). Therefore, identification of factors associated with longer duration of status epilepticus may provide the foundations for the development of interventions that could improve the outcome of status epilepticus by reducing seizure length.

In this chapter, through a prospective, paediatric, population based study, the frequency, aetiology, seizure characteristics and outcome of CSE in childhood are described and the following specific research questions are addressed:

1. What is the incidence, occurrence, aetiology and seizure characteristics of childhood CSE?

2. What is the relationship between ethnicity, socioeconomic status, age and incidence of childhood CSE?

3. What are the factors associated with CSE lasting longer than 60 minutes compared to CSE lasting 30-60 minutes?

4. What is the one year risk of recurrence of CSE?

5. What is the short term mortality associated with CSE?

5.2 Methods

5.2.1 Data collection tools

5.2.1.1 The questionnaire (admission proforma)

In order to increase the accuracy of the clinical history and treatment of episodes of CSE, a questionnaire was developed. This was to be used at the time of presentation to hospital with the intention that it would serve as an admission proforma for children with CSE. The questionnaire was revised following consultation with members of the Steering Committee and piloted for 6 weeks in Tübingen, Germany, among children with convulsive status epilepticus who were admitted to the University Hospital of Tübingen. The revised draft was sent to all members of the Collaborative Group for individual comments and further discussed at a Collaborative Group meeting. The final product, Appendix 10 was the final consensus view of the Collaborative Group.

5.2.1.2 Systems for identification of cases of CSE

These were described in detail in Chapter 4.

5.2.2 Data management

In consultation with a database designer, a linked anonymised system for data storage, management and analysis was developed. All patient identifiable information and patient clinical data were stored in separate but linked databases designed in Microsoft Access 97. Patient identifiable information (PII) were entered into a password protected, electronic database held on a networked computer with access limited to the principal researchers and secured in a lockable room. Clinical data on patients were entered into a separate password protected, electronic database held on a non-networked computer with access limited to the principal researchers and kept in a separate lockable room from that which will held the PII database. Database passwords were changed at least six-monthly and electronic back up files were created at least weekly. Anonymised paper copies of admission proformas were stored in a lockable room. All confidential correspondence/data were shredded. Every effort was taken to safeguard patient confidentiality.

5.2.3 Pilot phase of the project

The first three months of the project served as a pilot phase. Initially, accident and emergency physicians and neurophysiologists were also included in the BPSU-like surveillance scheme to prevent missed cases. However during the study it became apparent that all children with CSE would be referred to paediatric services and after three months following a Steering Group meeting, only paediatricians were sent monthly surveillance forms. In order to safeguard confidentiality, it was proposed in the initial study design that the principal researchers would collect data on the event through a structured telephone interview with the referring physician. During the study, it became evident that this was neither effective nor efficient and the data

collection methodology was reviewed. After consultation with the Collaborative Group and the Steering Group, it was decided that the admission proforma would remain unchanged but data collection would principally be through examination of anonymised copies of admission proformas faxed to a secure number at the NLSTEPSS coordinating centre, with direct interviews (by telephone or face to face) with the medical, nursing, accident and emergency, or paramedics by the candidate if further information were necessary.

5.2.4 Ethical Approval

All committees that gave ethical approval of the study agreed with the candidate's proposal that consent for entry into the study was not required. Verbal or written consent for inclusion in the study was not considered mandatory because:

1) NLSTEPSS was a non-interventional, surveillance study,
2) the data to be collected were part of standard information that should be obtained on children with CSE,
3) for research purposes, no direct contact was to be made between the researcher and the patients or their families.

As the candidate had clinical duties within the neurology service at one of the 22 hospitals involved in the research, Great Ormond Street Hospital for NHS Trust, occasionally at Great Ormond Street Hospital for NHS Trust, the candidate had direct contact with children referred to the neurology service because of CSE. Such patients were included in the study but, as in every other patient in the study, every effort was made to safeguard patient confidentiality. Thus, only the minimum data required to identify patients were obtained and stored from notifications to NLSTEPSS.

Furthermore, all patient data were handled in accordance with the principles of the Caldicott Committee Report on the Review of Patient-Identifiable Information, those contained in the Data Protection Act 1991 and those outlined in the BPSU's Guidance Statement on Patient Confidentiality. Patients eligible for inclusion in NLSTEPSS, were assigned a unique study identification number that was shared with NLSTEPSS research collaborators at their local hospital. All patient data stored in NLSTEPSS were anonymised but identifiable through study identification numbers. To facilitate possible follow up studies on the cohort of patients identified in NLSTEPSS, collaborators were asked to keep a record of study identification numbers of patients along with their demographic details. Copies of the study protocol were included in all applications to ethics committees. NLSTEPSS was approved by the London Multicentre Research Ethics Committee, a central ethics committee that considers applications for studies to be conducted in more than four hospitals. Ethical approval of the study was also given by Local Research Ethics Committees of all 22 hospitals involved in the study.

5.2.5 Definitions

5.2.5.1 *Convulsive status epilepticus* was strictly defined as a seizure with focal or generalised motor manifestations, or series of such seizures between which consciousness is not regained, which last for at least 30 minutes (Commission on the Terminology of the International League Against Epilepsy 1981; International League Against Epilepsy 1993). Children with CSE for whom fever was the only precipitant identified were included in the study. The following were excluded:

a) episodes where there was insufficient documentation to confirm a seizure or series of seizures of duration of at least thirty minutes

b) seizures that lasted less than 30 minutes whether the seizures were terminated by emergency anti-epileptic drugs or not

c) multiple seizures during a 24 hour period each lasting less than 30 minutes and with periods of lucidity in between seizures

d) episodes of NCSE (seizure activity without significant clinical features but with EEG changes consistent with SE).

5.2.5.2 North London. North London was defined as in Chapter 3. Children whose primary home address was outside of North London were excluded.

5.2.5.3 Age. All patients aged less than 16 years, excluding neonates, were included in NLSTEPSS. The characteristics of neonatal seizures differ greatly from seizures in older children and convulsive status epilepticus is rare in neonates. Therefore, neonates were excluded from the study.

5.2.5.4 Ethnicity. For each child clinical and demographic data, including ethnicity and home postcode were collected. All data were anonymised before analysis. As part of the regular hospital admission process, parents were asked to indicate the ethnicity of their child from a list of ethnic groups. The ethnic group categories were those used in Census 2001: White, Black, Asian, Other (includes mixed ethnicity).

5.2.5.5 Socioeconomic Status. Home postcodes for each child were used to determine an Index of Multiple Deprivation 2004 (IMD 2004) score of socioeconomic deprivation for the local area (SOA) in which the child lived. The method of determining an IMD 2004 score using an individual's home postal code was described in Chapter 3.

5.2.5.6 Aetiologies. Aetiologies of CSE were categorised using a modified version of the ILAE's recommended classification system. As discussed in Chapter 1, Section 1.3, in order to identify factors associated with prolonged febrile seizures that may lead to pathophysiological hypotheses on their mechanisms, there is an argument for considering prolonged febrile seizures as a distinct category of status epilepticus. For the purposes of NLSTEPSS, prolonged febrile seizure was considered as a distinct category. In addition, the designation "acute on remote symptomatic SE" was included in order to distinguish those children with previous neurological abnormalities with fever and illness related seizures, from those with prolonged febrile seizures. See Table 5.1 for details of the classification of aetiologies of CSE used in NLSTEPSS. Aetiologies were classified by the candidate and one of the candidate's supervisors. Disagreements in classification were resolved by consensus or by third part adjudication.

1. Prolonged Febrile Seizure – CSE in a previously neurologically normal child aged between 6 months and five years during a febrile (temperature above 38 ^{0}C) illness and in the absence of defined central nervous system (CNS) infection.

2. Acute symptomatic - CSE in a previously neurologically normal child, within a week of an identified acute neurological insult including head trauma, CNS infection, encephalopathy, cerebrovascular disease, metabolic derangements.

3. Remote symptomatic - CSE in the absence of an identified acute insult but with a history of a pre-existing CNS abnormality more than 1 week before.

4. Acute on remote symptomatic - CSE that occurred within a week of an acute neurological insult or febrile illness and occurred in a child with a history of previous neurological abnormality, including epilepsy. This category included children with cerebral palsy with a febrile illness not of CNS origin, and children with obstructed ventriculo-peritoneal shunts for hydrocephalus.

5. Idiopathic Epilepsy related - CSE that is not symptomatic and occurred in children with a prior diagnosis of idiopathic epilepsy or when the episode of CSE is the second unprovoked seizure that has led to a diagnosis of idiopathic epilepsy.

6. Cryptogenic Epilepsy related - CSE that is not symptomatic and occurred in children with a prior diagnosis of cryptogenic epilepsy or when the episode of CSE is the second unprovoked seizure that has led to a diagnosis of cryptogenic epilepsy.

7. Unclassified - CSE that cannot be classified into any other group.

Table 5.1: NLSTEPSS classification system of the aetiologies of CSE in childhood.

The following acute symptomatic aetiologies were associated with CSE in the study: (1) *acute bacterial meningitis*, (2) *viral CNS infections*, (3) *acute metabolic*: any systemic dysfunction that resulted in metabolic disturbances including electrolyte imbalance, hypoglycaemia, or other metabolic abnormalities, (4) *drug related*: included adverse drug reactions and drug overdoses, (5) *head injury*: injury requiring medical treatment or hospitalisation, (6) *hypoxia/anoxia*: respiratory insufficiency as indicated by central cyanosis and decreased oxygen saturation or decreased oxygen levels on blood gases or documented respiratory or cardio-respiratory arrest lasting at least 5 minutes preceding CSE, (8) *fever*: fever as the only identified precipitant but outside of the defined age range for prolonged febrile seizures could not be fulfilled. (9) *cerebrovascular accident* (CVA): included occlusive, embolic or haemorrhagic infarction.

Epilepsy was defined as two or more unprovoked seizures in a lifetime. Within the idiopathic/ cryptogenic epilepsy related aetiology categories, the following sub-categories were also used: (1) epilepsy diagnosed before CSE, (2) epilepsy diagnosed at the time of CSE (CSE was the second unprovoked seizure that led to the diagnosis of epilepsy) and (3) epilepsy diagnosed after CSE (CSE was the first unprovoked seizure and subsequent seizures led to the diagnosis of epilepsy). Two month follow up data on seizure recurrence and results of epilepsy investigations were available for all patients who had a first unprovoked seizure. If the diagnosis of epilepsy was made within two months of the initial episode of CSE, for the purposes of this study, CSE was considered as the first unprovoked seizure that led to the diagnosis of epilepsy.

5.2.5.7 *Seizure types.* The classification of CSE seizure type was based on the criteria of the International League Against Epilepsy as: primary generalised, focal with secondary generalisation and focal (International League Against Epilepsy 1993; Engel 2001). Generalised CSE types were subtyped into tonic, clonic and tonic-clonic seizures. Focal with secondarily generalised CSE included cases with focal features and whose final seizure type was tonic, clonic, or tonic-clonic. Focal CSE included those cases with motor seizures that did not generalise. Episodes of CSE that were a single seizure were characterised as continuous CSE and those that were serial seizures without recovery of consciousness between seizures were characterised as intermittent CSE.

Seizure types were classified independently by the candidate and one of the candidate's supervisors. Disagreements in classification were resolved by consensus or by third part adjudication. The classification of seizure type was based on review of the documented description of events by the attending physicians on a standardised data collection form that also served as the hospital admission notes (the admission proformas) and through direct interview with attending paediatricians, emergency physicians, paediatric intensivists, paediatric neurologists, nurses, paramedics or members of the research team. Direct interview with parents was possible when a member of the research team was also the attending paediatrician, emergency physicians, paediatric intensivists, or paediatric neurologists. Where indicated, anonymised copies of the A&E, nursing, ambulance and intensive care notes were also reviewed. Most cases were notified to and evaluated by the research team within five days of the diagnosis.

5.2.5.8 Incident cases. Incident cases were defined as lifetime first episodes of CSE.

5.2.5.9 Occurrence cases. Occurrence cases were defined as any case of CSE during the study period.

5.2.5.10 Recurrence. Children who had an incident episode of CSE during the first year and had at least one further episode of CSE, during the second year of the study were defined as having a recurrence of CSE. Recurrent episodes of CSE during a single admission were included.

5.2.5.11 Duration. Data on duration of CSE were obtained using the method for data collection for classification of seizure types described above. The admission proforma included the clock time noted by the parents at the first recognition of the seizure, the time the ambulance was called, time the ambulance arrived to the child, time of arrival to A&E and clock time of cessation of overt clinical seizure activity. When doubt existed, the shorter duration of seizure was used. Duration was defined as the interval between onset of CSE and cessation of clinical seizure activity.

5.2.5.12 Mortality. Mortality was defined as death associated with CSE, occurring during hospitalisation for CSE. All patients were followed up during hospitalisation or to the time of death. Survival was defined as alive following hospitalisation.

5.2.6 Case identification

The methods of identification of possible cases of CSE cases were described in Chapter 4. In the period May 1, 2002 to April 31, 2004, each reported case of CSE

was evaluated by the research team to verify fulfilment of inclusion criteria for the study i.e. residence in North London, aged less than 16 years and whether they met the strict definition of CSE or not. Residence within North London was validated by documenting children's home postal code against an electronic database of postal codes within North London. Most cases (70%) that were excluded were children who resided outside of North London. Twenty percent of those excluded did not meet the definition of CSE; the remainder were outside the age range. Only the minimum information required to identify the patients whilst safeguarding confidentiality was requested of notifications.

5.2.7 Data collection

Once eligibility for the study was confirmed, each child was assigned a unique study identification number (study ID) that was given to the local researcher at the referring hospital. All subsequent data on each child were anonymised, using the study ID as the unique patient identifier. Local researchers were asked to keep a record of all patients notified to NLSTEPSS along with their assigned study ID to facilitate any subsequent follow up studies. Data on each eligible case were obtained in two phases. In the initial phase, data was obtained through review of anonymised copies of the standardised admission proforma during hospitalisation or within 2 weeks of notification. Where necessary, supplemental information was obtained through review of anonymised copies of A&E, nursing, ambulance and intensive care notes. Direct interview with attending paediatricians, emergency physicians, paediatric intensivists, paediatric neurologists, nurses, paramedics and parents facilitated a more accurate and detailed account of the clinical course and treatment of the CSE event. In the second phase of data collection, conducted six to eight weeks after the first phase, results for

investigations not available during the first phase were obtained through local collaborators. All data on each CSE event were entered into a Microsoft Access 97 database and included demographic data, detailed seizure history, seizure duration, previous medical history, perinatal history, development history, family history of seizures, details of treatment of CSE, aetiology of CSE, results of laboratory investigations and outcome.

5.2.8 Database validation

The data from audits in randomly selected hospitals described in Chapter 4 served to validate the information in the database.

5.2.9 Maintaining the interest of local collaborators

There were three collaborator's meetings over the study period, but the candidate corresponded at least every two months by telephone and or e-mail with each collaborator giving updates on progress of the research, presentations at international, national conferences and papers arising from the research. In addition, collaborators were regularly sent cards and occasionally token gifts of wine for festive occasions (Christmas, Easter, anniversary of commencement date of the study).

5.2.10 Statistics.

Data analyses were conducted in SPSS Version 10 (Chicago, Illinois), Microsoft Office Excel 2003, Intercooled Stata 6.0, CARE-1 and StatXact v4.0.1. The degree of ascertainment of the study was investigated through a three source capture-recapture model using CARE-1 software in S plus (Chao et al., 2001). Details of the method were described in Chapter 4.

The average annual incidence and occurrence of CSE for North London children between the period May 1, 2002 to April 31, 2004, were estimated using population data from UK Census 2001 as denominator and the average number of incident and occurrence cases per year as numerator. Crude, ascertainment adjusted, age-adjusted, ethnicity-adjusted, age-specific and ethnicity-specific, incidence and occurrence rates by sex, seizure type, duration and aetiology were calculated.

Age-adjusted and ethnicity-adjusted estimates were determined by directly adjusting crude estimates to the UK Census 2001 England and Wales paediatric population (Office of National Statistics 2004a; Office of National Statistics 2004b).

The relationships between incidence and age, socioeconomic status and ethnicity were investigated using Poisson multivariate regression analysis. To examine possible interaction effects of socioeconomic status with ethnicity/age, two way and three way interaction terms were tested in the multivariate analysis.

Predictors for factors associated with a duration of CSE greater than 60 minutes were investigated through forward stepwise multivariate logistic regression analysis with subsequent removal of nonsignificant variables with significant levels for entering and removing variables set at $p=0.05$ and $p=0.1$ respectively. The following variables were investigated: age, ethnicity, sex, socioeconomic status, prehospital treatment or not, interval between onset of CSE and arrival to A&E, treatment with emergency AED within 10 minutes of onset of CSE, treatment with emergency AED within 15 minutes of onset of CSE, adequacy of first dose of AED, incident vs non-incident

episode, treatment with more than 2 doses of benzodiazepines, focal features, febrile or not, intermittent vs continuous CSE and neurological state prior to episode of CSE. Only first episodes of all children who had CSE during the study period were included in the analysis on factors associated with duration of CSE greater than 60 minutes.

5.3 Results

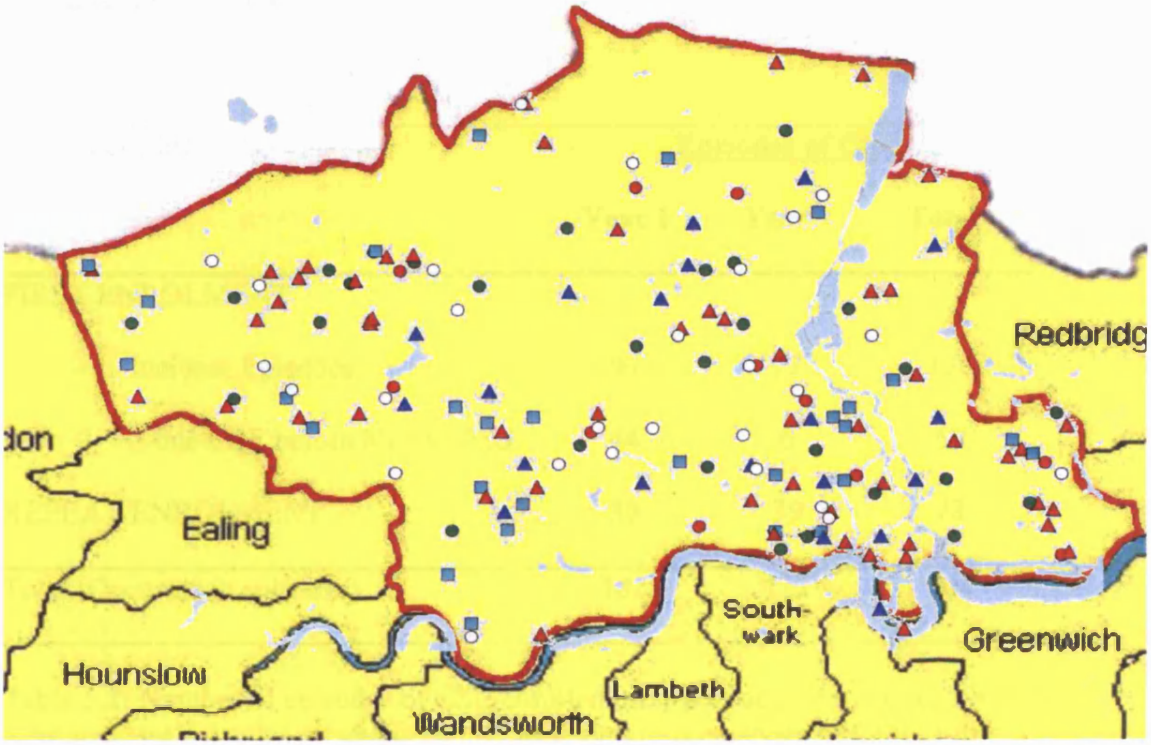

Figure 5.1: Map of North London (area enclosed by red border) with distribution of incident cases of CSE from NLSTEPSS.

- Prolonged Febrile Convulsions
- Acute Symptomatic CSE
- Remote Symptomatic CSE
- Acute on Remote Symptomatic CSE
- Idiopathic/Cryptogenic Epilepsy Related CSE
- Unclassified

5.3.1 Demographics

There were 226 children with 304 episodes of CSE (occurrence episodes) notified to NLSTEPSS between May 1, 2002 and April 31, 2004. Of these children, 176 children had lifetime first (incident) episodes of CSE. There were 99 incident episodes of CSE in the first year of the study and 77 incident episodes in the second year. For further details on the number of episodes of CSE enrolled into the study each year, according to whether they were incident episodes or whether there were previous episodes of CSE, see Table 5.2.

Enrolment into NLSTEPSS	**Episodes of CSE**		
	Year 1	**Year 2**	**Total**
FIRST ENROLMENT			
Incident Episodes	99	77	176
≥ one CSE before NLSTEPSS	44	6	50
REPEAT ENROLMENT	39	39	78
Total (Occurrence episodes)	182	122	304

Table 5.2: Number of episodes of CSE enrolled each year according to whether they were incident episodes or whether there were previous episodes of CSE. Fifty children who were initially enrolled in the study had at least one previous episode of CSE before NLSTEPSS. Each year there were 39 repeat episodes of CSE following initial enrolment.

Amongst incident episodes of CSE, 136 (77%) started out of hospital whilst 40 commenced in hospital. This pattern was consistent for all occurrence episodes of CSE as amongst all CSE episodes, 240 episodes (79%) started out of hospital. Most children with CSE of out of hospital onset (83%) were taken to hospital by ambulance and the majority (97%) of children in the study presented to hospitals located within

the boundaries of North London. The distribution of incident episodes of CSE according to aetiology is illustrated in Figure 5.1

5.3.2 Notifications

Over the two year study period, of the 176 incident cases notified, 146 were notified by PHONE, 92 by FORMS and 62 by both PHONE and FORMS.

5.3.3 Regional BPSU-like Surveillance Scheme

The mean monthly proportion of responders (74%) to the BPSU-like surveillance scheme was similar for both years of the study. Paediatricians based outside of North London (6%) and general paediatricians (6%) and paediatric intensivists (4%) in North London were the main groups of non-responders. For further details on the proportion of non-responders according to paediatric subspecialty and location of their hospital, see Figure 5.2.

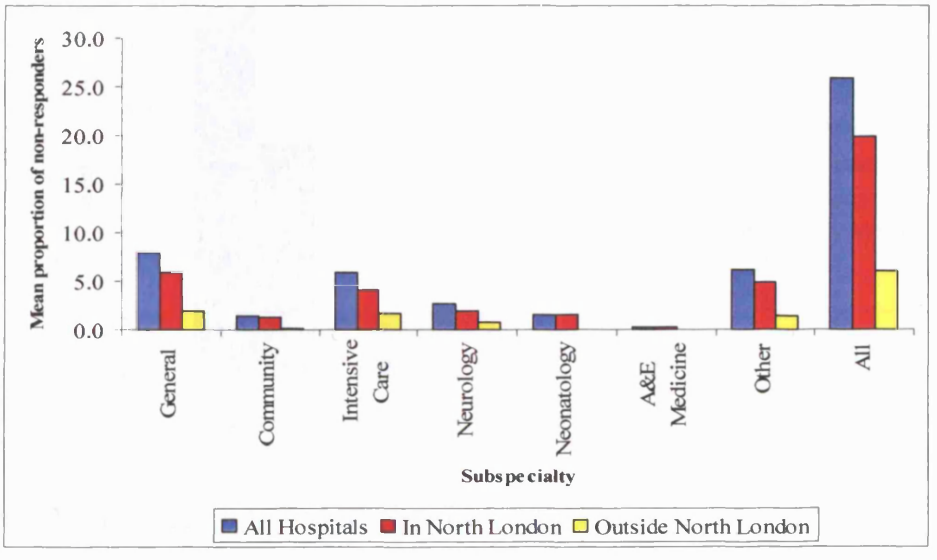

Figure 5.2: Mean proportion of non-responders according to sub-specialty and location of their hospital.

5.3.4 The incidence and occurrence of CSE in North London

The crude incidence of CSE in childhood in North London is 14.5/100,000 children per year and the crude occurrence is 25.1/100,000 children /yr.

5.3.5 Age-specific incidence of CSE

The incidence of CSE is highest among children aged less than 1 year of age compared to those aged 1 to 4, 5 to 9 and 10 to 15 years of age (see Table 5.3). This pattern is consistent for prolonged febrile seizures, acute symptomatic, remote symptomatic, acute on remote symptomatic and cryptogenic epilepsy related CSE but not for idiopathic epilepsy related or unclassified CSE. In the latter categories, children aged 1- 4 have the highest incidence. The high incidence of CSE in those aged less than a year is particularly marked in the acute symptomatic group in which acute CNS infections account for half of cases (see Figure 5.3).

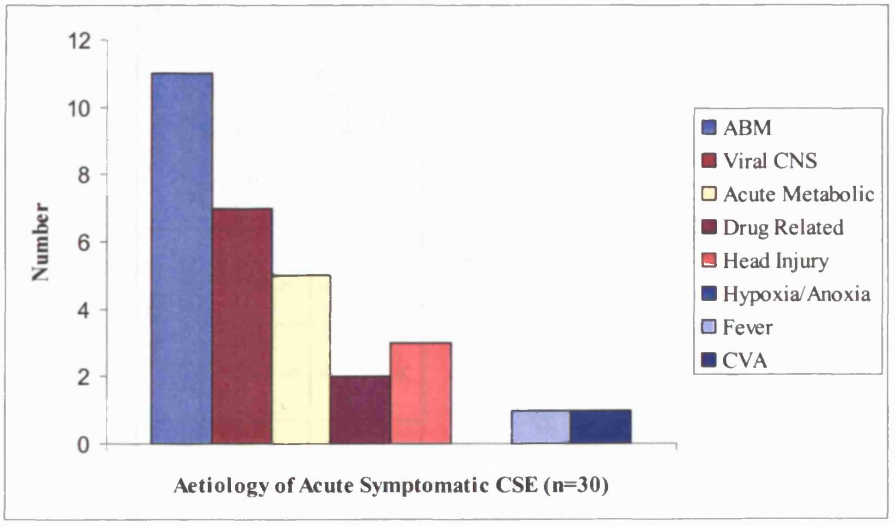

Figure 5.3: Aetiology of Acute Symptomatic CSE.

ABM = acute bacterial meningitis Viral CNS = viral CNS infection
Acute Metabolic = acute metabolic disturbance CVA = cerebrovascular accident

Age (y)	Population	Prolonged Febrile Seizure		Acute Symptomatic		Remote Symptomatic		Acute on Remote Symptomatic		Idiopathic Epilepsy Related		Cryptogenic Epilepsy Related		Unclassified		Total Group	
		N	I	N	I	N	I	N	I	N	I	N	I	N	I	N	I
<1	41397	15	18.1	14	16.9	4	4.8	5	6.0	1	1.2	2	2.4	1	1.2	42	50.7
1 - 4	161056	41	12.7	8	2.5	12	3.7	17	5.3	8	2.5	0	0.0	8	2.5	94	29.2
5 - 9	187261	0	0.0	6	1.6	8	2.2	5	1.3	8	2.1	1	0.3	3	0.8	31	8.3
10 - 15	215606	0	0.0	2	0.5	5	1.1	1	0.2	1	0.2	0	0.0	0	0.0	9	2.1
All	605320	56	4.6	30	2.5	29	2.4	28	2.3	18	1.5	3	0.2	12	1.0	176	14.5

Table 5.3: Age-specific number and incidence rate per 100,000 children/yr for CSE in childhood by aetiology for North London.

N = number I = incidence rate per 100,000 children/year

5.3.5.1 Age-specific incidence of CSE and sex.

The incidence of CSE is greater in males aged less than 1 year and 1 to 4 years of age compared to females of similar ages but across other age groups, males and females have similar incidence (see Figure 5.4).

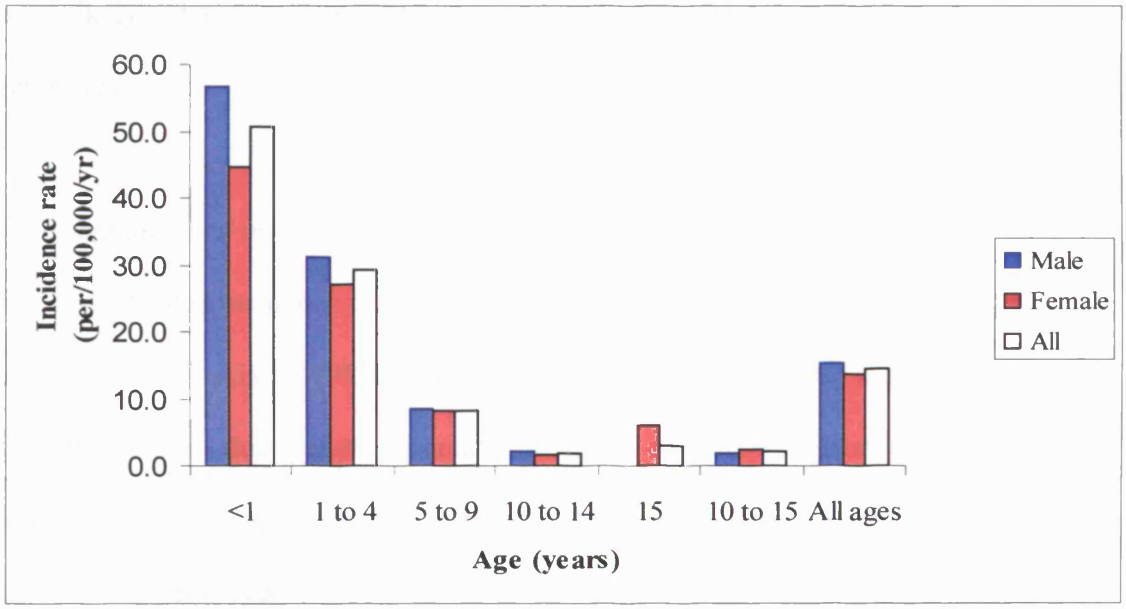

Figure 5.4: Age-specific incidence rate of convulsive status epilepticus in childhood by sex in North London.

5.3.5.2 Age-specific incidence of CSE and seizure characteristics

Throughout the age-spectrum, focal onset of CSE is common (a third of all cases) but few remain focal (8%). The incidence of primary generalized CSE is twice that of any other seizure type and the incidence of intermittent and continuous CSE is similar among all age groups. Most seizures are tonic-clonic in nature and the incidence of tonic CSE peaks in children less than 1 year of age. CSE is not usually associated with epilepsy; 88% of CSE occur in the absence of epilepsy. When CSE is associated with epilepsy, there is a history of epilepsy in 62% of incident cases, or it is the second seizure (29%) or first seizure (10%) leading to the diagnosis of epilepsy. For further details on age specific incidence and seizure characteristics, see Table 5.3.

Amongst children aged less than 5 years of age, the incidence of CSE in those who are previously normal is 1.6 (95% CI 1.1-2.3, p=0.042) times that of those who have previous neurological abnormalities, but in older children (5-15 years), children with pre-existing neurological abnormalities are 4.1(95% CI 1.8- 6.5, p = 0.005) times more likely to have incident CSE compared to those with previously normal neurology.

5.3.6 Age-adjusted incidence

The age-adjusted incidence of CSE is 13.2/100,000 children/yr. The age adjusted incidence in males is 1.2 (95% CI 1.0 – 1.3, p = 0.05) times greater than in females. This difference is due in part to a greater incidence of prolonged febrile seizures and acute on remote symptomatic CSE among males compared to females. In males, the incidence of prolonged febrile seizures is 4.5/100,000/yr (95% CI 3.7 -5.1/100,000/yr) compared with 3.1/100,000/yr (95% CI 2.6 -3.6/100,000/yr) among females. The incidence of acute on remote symptomatic CSE among males is 2.5/100,000/yr (95% CI 2.1 - 2.9/100,000/yr) versus 1.5/100,000/yr (95% CI 1.2 – 1.8/100,000/yr) among females. By definition, prolonged febrile seizures occur in children aged less than 6 years. Despite this, the age-adjusted incidence of prolonged febrile seizures is still greater than each of the other aetiologies of CSE. Higher incidence of CSE is seen in children who are previously neurologically normal or had acute on remote symptomatic CSE compared to other aetiologies of CSE. Clonic (0.1/100,000/yr) and tonic (1.6/100,000/yr) CSE occurs infrequently when compared to tonic clonic (11.5/100,000/yr) CSE. The age-adjusted incidence of primary generalized CSE is greater than each other seizure types. (For further details on age-adjusted incidence and seizure characteristics, see Table 5.4).

	Age (y)												
	<1		1 – 4		5 – 9		10 – 15		0-15			Age-adjusted incidence	
	N	I	N	I	N	I	N	I	N	I	95% CI		95% CI
AETIOLOGY													
PFS	15	18.1	41	12.7	0	0.0	0	0.0	56	4.6	(2.8 – 6.4)	4.1	(3.7 - 4.8)
Acute Symp	14	16.9	8	2.5	5	1.4	2	0.5	30	2.5	(1.3 – 3.6)	2.2	(1.9 - 2.5)
Remote Symp	4	4.8	12	3.7	8	2.2	5	1.1	29	2.4	(1.2 – 3.6)	2.3	(2.0 - 2.6)
Acute on Remote	5	6.0	17	5.3	5	1.4	1	0.2	28	2.3	(1.1 - 3.5)	2.1	(1.8 - 2.4)
Idiopathic	1	1.2	8	2.5	8	2.2	1	0.2	18	1.5	(0.5 - 2.5)	1.4	(1.2 - 1.7)
Cryptogenic	2	2.4	0	0.0	1	0.3	0	0.0	3	0.2	(-0.1 - 0.6)	0.2	(0.1 - 0.3)
Unclassified	1	1.2	8	2.5	4	1.1	0	0.0	12	1.1	(0.2 - 1.9)	1.0	(0.8 - 1.2)
EPILEPSY													
No epilepsy	39	47.1	86	26.7	22	6.1	8	1.9	155	12.8	(10.0 - 15.7)	11.7	(11.0 - 12.3)
Before SE	3	3.6	2	0.6	7	1.9	1	0.2	13	1.1	(0.2 - 1.9)	1.1	(0.9 - 1.2)
At SE	0	0.0	6	1.9	0	0.0	0	0.0	6	0.5	(-0.1 - 1.1)	0.4	(0.3 - 0.6)
After SE	0	0.0	0	0.0	2	0.6	0	0.0	2	0.2	(-0.2 - 0.5)	0.2	(0.1 - 0.3)
SEX													
Male	24	56.6	51	31.2	16	8.4	4	1.8	95	15.4	(11.0 - 19.8)	14.0	(13.0 - 15.0)
Female	18	44.5	43	27.1	15	8.2	5	2.4	81	13.6	(9.4 - 17.8)	12.5	(11.5 - 13.4)
ONSET													
Focal	16	19.3	33	10.2	11	3.0	3	0.7	63	5.2	(3.4 - 7.0)	4.8	(4.3 - 5.2)
Gen	25	30.2	61	18.9	20	5.5	6	1.4	112	9.3	(6.8 - 11.7)	8.5	(7.9 - 9.1)
Total	42	50.7	94	29.2	31	8.6	9	2.1	176	14.5	(11.5 - 17.6)	13.3	(12.6 - 14.0)
CHARACTER													
Continuous	19	22.9	47	14.6	14	3.7	4	0.9	84	6.9	(4.8 – 9.0)	6.3	(5.8 – 6.8)
Intermittent	23	27.8	47	14.6	17	4.5	5	1.2	92	7.6	(5.4 – 9.8)	6.9	(6.4 – 7.4)

	Age (y)												
	<1		1 – 4		5 – 9		10 – 15		0-15			Age adjusted incidence	
	N	I	N	I	N	I	N	I	N	I	95% CI		95% CI
FINAL SEIZURE TYPE													
Focal	2	2.4	5	1.6	2	0.6	0	0.0	9	0.7	(0.1 - 1.4)	0.7	(0.5 - 0.8)
Second Gen	14	16.9	26	8.1	9	2.5	3	0.7	52	4.3	(2.6 - 5.9)	3.9	(3.6 - 4.3)
Primary Gen	26	31.4	63	19.6	20	5.5	6	1.4	115	9.5	(7.0 - 12.0)	8.7	(8.2 - 9.3)
MOTOR TYPE													
Tonic	8	9.7	10	3.1	3	0.8	2	0.4	23	2.0	(0.8 -3.2)	1.6	(1.2 - 1.8)
Clonic	0	0.0	2	0.6	0	0.0	0	0.0	2	0.2	(-0.2 - 0.5)	0.1	(0.1 - 0.2)
Tonic Clonic	34	41.1	82	25.5	28	7.7	7	1.6	151	12.5	(9.7 - 15.3)	11.5	(10.8 - 12.1)
DURATION (mins)													
30 – 60	17	20.5	36	11.2	17	4.7	1	0.2	71	5.9	(3.9 - 7.8)	5.4	(4.9 - 5.8)
61 – 90	12	14.5	20	6.2	6	1.7	3	0.7	41	3.4	(1.9 - 4.9)	3.1	(2.8 - 3.4)
91 – 120	3	3.6	19	5.9	3	0.8	3	0.7	28	2.3	(1.1 - 3.5)	2.1	(1.9 - 2.4)
> 120	10	12.1	19	5.9	5	1.4	2	0.5	36	3.0	(1.6 - 4.3)	2.7	(2.4 - 3.0)
ALL	42	50.7	94	29.2	31	8.6	9	2.1	176	14.5	(11.5 - 17.6)	13.3	(12.6 - 14.0)

Table 5.4: Number, age–specific and age-adjusted incidence per 100,000 children per year according to features of incident episodes of CSE in North London. Age-adjusted to the 2001 England and Wales childhood population.

N = number I = incidence rate per 100,000 children/year.
PFS = Prolonged Febrile Seizure, Acute Symp = Acute Symptomatic, Remote Symp = Remote Symptomatic, Acute on Remote = Acute on Remote Symptomatic, Idiopathic = Idiopathic Epilepsy Related, Cryptogenic = Cryptogenic Epilepsy Related, Second Gen = Secondarily generalised, Primary Gen = Primary generalised

5.3.7 Socioeconomic status, age, ethnicity and incidence of CSE

Socioeconomic deprivation, younger age and non-white ethnicity are independently associated with an increased incidence of CSE. For each one point increase in the Index of Multiple Deprivation 2004, there is a cumulative increased risk of CSE by 3%. The younger age group 0-4 is more susceptible than older age groups. Children of Asian and children of other non-white ethnicity, but not black children are more likely to have an incident of CSE compared to white children. The incidence of CSE in black children is not different from that in white children (see Table 5.5).

Variable		Incidence Coefficient	*p*	95% CI
IMD 2004		1.03	0.003	1.01 – 1.04
Age				
	0-4	1.00 (reference)		
	5-7	0.30	<0.0005	0.19 – 0.47
	8-9	0.16	<0.0005	0.08 – 0.33
	10-15	0.06	<0.0005	0.03 – 0.12
Ethnicity				
	White	1.00 (reference)		
	Black	1.30	0.230	0.85 – 2.01
	Asian	2.06	<0.0005	1.43 – 2.97
	Other	1.88	0.007	1.19 – 2.98

Table 5.5: Poisson multivariate regression of incidence of CSE according to socioeconomic deprivation index, age and ethnicity.

There is evidence that the effect of socioeconomic deprivation on the incidence of CSE is less in Asian children compared to white children but overall, there was no evidence that the effect of socioeconomic deprivation is different amongst ethnic groups (see Table 5.6).

Variable		Incidence Coefficient	*p*	95% CI
IMD 2004		1.03	0.007	1.01 – 1.06
Age				
	0-4	1.00 (reference)	-	-
	5-7	0.30	<0.0005	0.19 – 0.47
	8-9	0.16	<0.0005	0.08 – 0.32
	10-15	0.06	<0.0005	0.03 – 0.12
Ethnicity				
	White	1.00 (reference)	-	-
	Black	1.22	0.83	0.21-7.14
	Asian	6.62	0.002	2.0 – 21.9
	Other	1.37	0.72	0.25-7.5
IMD 2004 * Ethnicity				
	IMD 2004* White	1.00 (reference)	-	-
	IMD 2004* Black	1.00	0.97	0.95 - 1.05
	IMD 2004* Asian	0.97	0.05	0.93 – 1.00
	IMD 2004* Other	1.01	0.71	0.96 – 1.06

Table 5.6: Poisson multivariate regression of incidence of CSE according to socioeconomic deprivation index, age, ethnicity, including two way interaction effects between socioeconomic deprivation index and ethnicity.

5.3.8 Ethnicity-specific incidence of CSE

The increased incidence of CSE in children of Asian ethnicity and children of other non-white ethnicity, but not black children, may be partly explained by the 4 times greater incidence of prolonged febrile seizures in children of Asian (8.1/100,000/yr, 95% CI 3.2-13.0/100,000/yr) and Other (8.5/100,000/yr, 95% CI 1.5-15.4) ethnic groups compared to white (2.5/100,000/yr, 95% CI 0.7 – 4.2/100,000/yr) children. The incidence of Remote symptomatic CSE peaks in Asian children and the incidence of Acute on Remote symptomatic CSE peaks in Asian and black children (See Figure 5.5). There is a trend towards longer duration of CSE in children of non-white ethnicity compared to white children. For further details on ethnicity specific incidence and features of CSE, see Table 5.5).

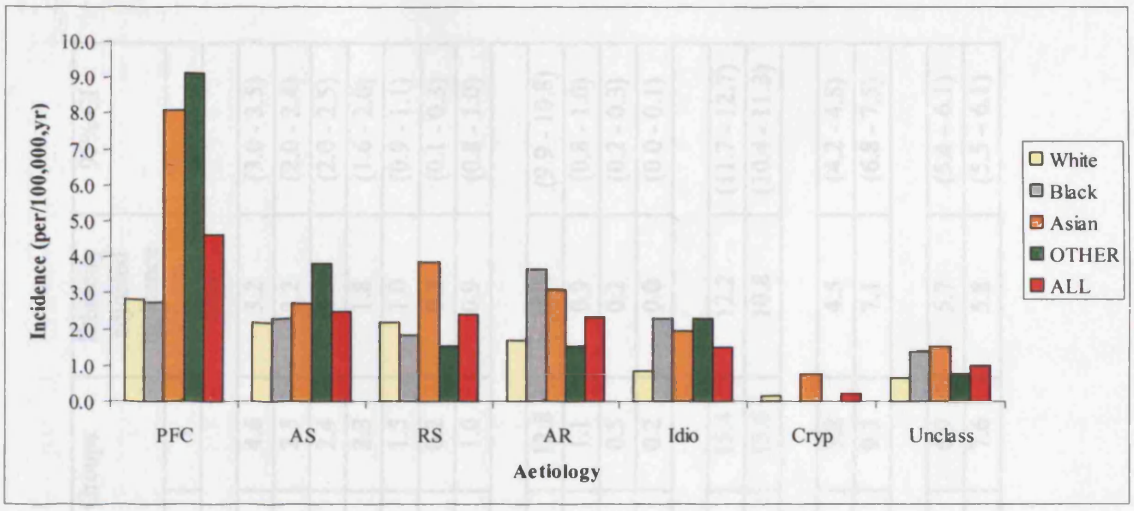

Figure 5.5: Ethnicity specific incidence of CSE according to aetiology.

PFS = Prolonged Febrile Seizure, Acute Symptomatic = Acute Symptomatic, Remote Symptomatic = Remote Symptomatic, Acute on Remote = Acute on Remote Symptomatic, Idiopathic = Idiopathic Epilepsy Related, Cryptogenic = Cryptogenic Epilepsy Related, Unclass = Unclassified

5.3.9 Ethnicity-adjusted incidence of CSE

The ethnicity-adjusted incidence of CSE in childhood is 11.5/100,000 children/yr (95% CI 11.1 - 12.0/100,000/yr). The highest ethnicity adjusted incidences are in prolonged febrile seizures and acute symptomatic CSE. As in age-adjusted incidence, the ethnicity-adjusted incidence of CSE is greater amongst males (12.2/100,000/yr, 95% CI 11.7 - 12.7/100,000/yr) compared to females (10.8/100,000/yr, 95% CI 10.4 – 11.3/100,000/yr). For further details on ethnicity-adjusted incidence and features of CSE, see Table 5.7).

	White		Black		Asian		Other		All Groups		Ethnicity adjusted incidence	95% CI
	N	I	N	I	N	I	N	I	N	I		
AETIOLOGY												
PFS	17	2.8	6	2.7	21	8.1	12	9.1	56	4.6	3.2	(3.0 - 3.5)
Acute Symptomatic	13	2.2	5	2.3	7	2.7	5	3.8	30	2.5	2.2	(2.0 - 2.4)
Remote Symptomatic	13	2.2	4	1.8	10	3.9	2	1.5	29	2.4	2.3	(2.0 - 2.5)
Acute on Remote	10	1.7	8	3.7	8	3.1	2	1.5	28	2.3	1.8	(1.6 - 2.0)
Idiopathic	5	0.8	5	2.3	5	1.9	3	2.3	18	1.5	1.0	(0.9 - 1.1)
Cryptogenic	1	0.2	0	0.0	2	0.8	0	0.0	3	0.2	0.2	(0.1 - 0.3)
Unclassified	4	0.7	3	1.4	4	1.5	1	0.8	12	1.0	0.9	(0.8 - 1.0)
EPILEPSY												
No epilepsy	57	9.5	26	11.9	50	19.3	22	16.7	155	12.8	10.4	(9.9 - 10.8)
Before SE	5	0.8	3	1.4	5	1.9	0	0.0	13	1.1	0.9	(0.8 - 1.0)
At SE	1	0.2	2	0.9	0	0.0	3	2.3	6	0.5	0.2	(0.2 - 0.3)
After SE	0	0.0	0	0.0	2	0.8	0	0.0	2	0.2	0.0	(0.0 - 0.1)
SEX												
Male	34	11.1	16	14.6	30	22.7	15	22.4	95	15.4	12.2	(11.7 - 12.7)
Female	29	9.9	15	13.8	27	21.2	10	15.4	81	13.6	10.8	(10.4 - 11.3)
ONSET												
Focal	26	4.3	14	6.4	16	6.2	7	5.3	63	5.2	4.5	(4.2 - 4.8)
Generalised	38	6.3	17	7.8	41	15.8	17	12.9	113	9.3	7.1	(6.8 - 7.5)
CHARACTER												
Continuous	32	5.3	16	7.3	24	9.3	12	9.1	84	6.9	5.7	(5.4 – 6.1)
Intermittent	31	5.2	15	6.9	33	12.7	13	9.9	92	7.6	5.8	(5.5 – 6.1)

	White		Black		Asian		Other		All Groups		Ethnicity adjusted incidence	
	N	I	N	I	N	I	N	I	N	I		
FINAL SEIZURE TYPE												
Focal	3	0.5	2	0.9	4	1.5	0	0.0	9	0.7	0.6	(0.5 - 0.7)
Second Gen	23	3.8	11	5.0	12	4.6	6	4.6	52	4.3	3.9	(3.7 - 4.2)
Primary Gen	37	6.2	18	8.2	41	15.8	19	14.4	115	9.5	7.1	(6.7 - 7.4)
MOTOR TYPE												
Tonic	10	1.7	3	1..5	6	2.3	4	3.0	23	2.0	1.8	(1.6 -2.0)
Clonic	1	0.2	0	0.0	0	0.0	1	0.8	2	0.2	0.2	(0.1 - 0.2)
Tonic-Clonic	52	8.7	28	12.8	51	19.7	20	15.2	151	12.5	9.6	(9.2 - 10.1)
DURATION (mins)												
30 – 60	33	5.5	13	5.9	17	6.6	8	6.1	71	5.9	5.6	(5.3 - 5.9)
61 – 90	13	2.2	7	3.2	19	7.3	2	1.5	41	3.4	2.5	(2.3 - 2.7)
91 – 120	4	0.7	5	2.3	10	3.9	9	6.8	28	2.3	1.1	(1.0 - 1.3)
> 120	13	2.2	6	2.7	11	4.2	6	4.6	36	3.0	2.4	(2.2 - 2.6)
ALL	63	10.5	31	14.2	57	22.0	25	19.0	176	14.5	11.5	(11.1 - 12.0)

Table 5.7: Number, ethnicity–specific and ethnicity-adjusted incidence per 100,000 children per year according to features of lifetime first episodes of CSE in North London. Ethnicity adjusted to the 2001 England and Wales childhood population.

N = number of cases I = incidence rate per 100,000 children/year.
PFS = Prolonged Febrile Seizure, Acute Symptomatic = Acute Symptomatic, Remote Symptomatic = Remote Symptomatic, Acute on Remote = Acute on Remote Symptomatic, Idiopathic = Idiopathic Epilepsy Related, Cryptogenic = Cryptogenic Epilepsy Related, Second Gen = Secondarily generalised, Primary Gen = Primary generalised

5.3.10 Boroughs and incidence

There is a wide range of incidence of CSE amongst boroughs within North London. Crude incidence ranges from 0/100,000 children/yr in the City of London (childhood population 673) to 26.7/100,000 children/yr in Tower Hamlets (borough with the highest mean socioeconomic deprivation score. With the exception of the borough of Newham, boroughs with higher mean socioeconomic deprivation scores (IMD 2004) and a higher proportion of non-white children were associated with higher incidence of CSE. For further details, see Table 5.8

5.3.11 Features of incident cases of CSE in North London

CSE lasts longer than an hour in a significant proportion (60%) of children with CSE, irrespective of the underlying aetiology. Focal onset of CSE is common (36%) but most episodes of CSE with a focal onset will secondarily generalise, as the final seizure type was focal in only 5% of incident cases. In children with CSE associated with fever, there is some evidence that focal features are more common in children with acute CNS infection than children with prolonged febrile seizures (8/18 vs 12/56 respectively, $p = 0.06$). The overwhelming majority of CSE in children is tonic-clonic (86%) in nature, with tonic CSE being the next most common (11%). For more details on the features of incident cases in North London, see Table 5.9.

Borough	Mean IMD 2004	Childhood Population	% White	% Black	% Asian	% Other	N	Incidence (per 100,000,yr)	95% CI
Barnet	16.09	63756	67	9	12	12	20	15.7	(6.0 - 25.4)
Brent	25.93	52169	30	28	30	11	20	19.2	(7.3 - 31.0)
Camden	34.65	32867	55	15	18	12	11	16.7	(2.7 - 30.7)
City Of London	15.32	673	67	4	18	12	0	0.0	(0 - 0)
Enfield	23.11	57793	69	14	8	8	11	9.5	(1.6 - 17.5)
Hackney	45.05	47430	47	30	12	11	17	17.9	(5.9 - 30.0)
Hammersmith & Fulham	27.79	27226	63	18	6	12	4	7.3	(-2.8 - 17.5)
Haringey	37.69	44605	51	29	7	13	12	13.5	(2.7 - 24.2)
Harrow	13.57	41691	47	9	33	10	16	19.2	(5.9 - 32.5)
Islington	42.66	32242	60	19	8	13	4	6.2	(-2.4 - 14.8)
Kensington & Chelsea	21.65	24795	68	12	6	14	1	2.0	(-3.6 - 7.6)
Newham	40.53	63841	25	26	40	9	18	14.1	(4.9 - 23.3)
Tower Hamlets	45.75	44890	50	7	62	6	24	26.7	(11.6 - 41.9)
Waltham Forest	30.25	46868	50	20	20	10	10	10.7	(1.3 - 20.0)
Westminster	31.66	24474	56	12	15	17	8	16.3	(0.3 - 32.4)
All		605320	47	19	22	11	176	14.5	(11.5 - 17.6)

Table 5.8: Mean IMD 2004 score, childhood population, ethnic composition, number of incident cases in the study period, and crude incidence of CSE according to boroughs within North London.

	Prolonged febrile seizures		Acute Symptomatic		Remote Symptomatic		Acute on Remote		Idiopathic		Cryptogenic		Unclassified		All	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
SEX																
Male	34	61	15	50	13	45	17	61	10	56	1	33	5	42	95	54
Female	22	39	15	50	16	55	11	39	8	44	2	67	7	58	81	46
DURATION (mins)																
30-60	27	48	11	37	12	41	8	29	8	44	0	0	5	42	71	40
61-90	9	16	6	20	9	31	8	29	5	28	2	67	2	17	41	23
91-120	9	16	6	20	3	10	6	21	1	6	0	0	3	25	28	16
>120	11	20	7	23	5	17	6	21	4	22	1	33	2	27	36	21
CHARACTER																
Continuous	32	57	13	43	14	48	12	43	8	44	0	0	5	48	84	48
Intermittent	24	43	17	57	15	52	16	57	10	56	3	100	7	52	92	52
ONSET																
Focal	12	21	14	47	9	31	15	54	4	22	1	33	6	50	63	36
Generalised	44	79	16	53	20	69	13	46	14	78	2	67	6	50	112	64
FINAL SEIZURE TYPE																
Focal	1	2	3	10	4	14	1	4	0	0	0	0	0	0	9	5
Second Generalised	11	20	11	37	5	17	14	50	4	22	1	33	6	50	52	30
Primary Generalised	44	79	16	53	20	69	13	46	14	78	2	67	6	50	115	65
MOTOR TYPE																
Tonic	3	5	7	24	2	7	5	18	1	6	1	33	4	33	23	13
Clonic	1	2	1	3	0	0	0	0	0	0	0	0	0	0	2	1
Tonic Clonic	52	93	22	73	27	93	23	82	17	94	2	67	8	67	151	86
ALL	56	100	30	100	22	100	28	100	18	100	3	100	12	100	176	100

Table 5.9: Features of life time first episodes of CSE in children in North London

5.3.12 Occurrence of CSE

The crude occurrence rate of CSE in childhood in North London is 25.1/100,000/yr. Similar to the incidence of CSE, the occurrence of CSE is greatest in those aged less than 5 years (54.6/100,000/yr, 95% CI 44.4 - 64.8/100,000/yr), particularly in those aged less than a year (64/100,000/yr, 95% CI 39.6-88.4/100,000/yr). The age-adjusted occurrence of CSE is 25.4/100,000/yr (95% CI = 22.5-28.2/100,000/yr). For details on age-specific occurrence rate of CSE see Table 5.10. The ethnicity –adjusted occurrence of CSE is 21.4/100,000/yr (95% CI = 20.8-22.0/100,000/yr.

Age (y)	Occurrence number	Population	Occurrence Rate (per 100,000/yr)	95% CI (per 100,000/yr)
<1	53	41397	64.0	39.6 – 88.4
1 to 4	168	161056	52.2	41.0 – 63.4
5 to 9	59	187261	15.8	10.1 – 21.5
10 TO 15	24	215606	5.6	2.4 – 8.8
All	304	605320	25.1	21.1 – 29.1

Table 5.10: Age–specific occurrence rate per 100,000 children per year.
Age-adjusted occurrence = 25.4/100,000/yr (95% CI = 22.5-28.2/100,000/yr).
Age-adjusted to the paediatric population of England and Wales 2001.

5.3.13 Ascertainment adjustment using capture-recapture

Over the 2 year study period, 73 incident episodes of CSE that presented to any of the six randomly selected hospitals from the research network were identified. Of these 62 were notified to NLSTEPSS by PHONE/FORM and 11 were only identified by the yearly reviews. For details of the number of cases identified by any of the three sources, please see Figure 5.6.

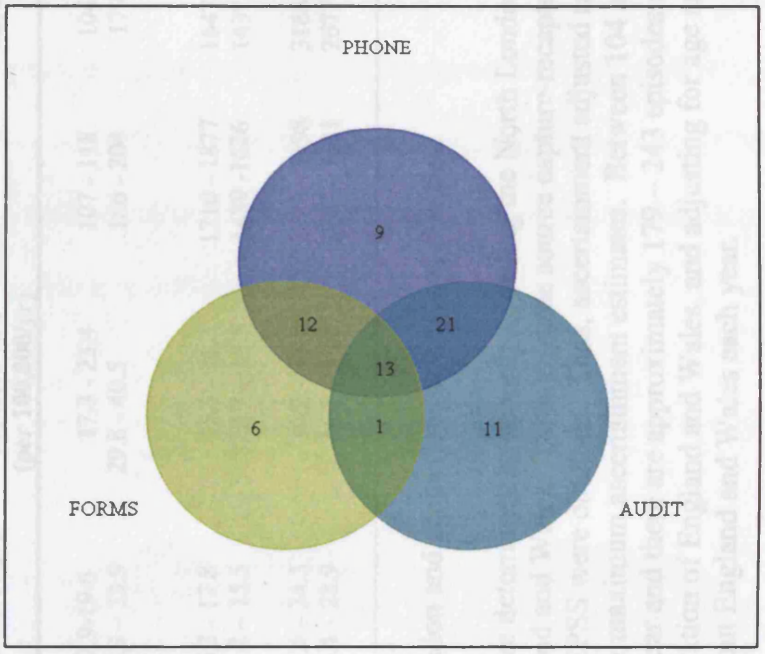

Figure 5.6: Number of incident episodes of CSE identified in 6 randomly selected hospitals in North London according to source of identification.

The three source capture-recapture estimate of the number of incident episodes of CSE that presented to the six randomly selected hospitals was 77-84 (95% CI 74 to 100). Case ascertainment at these 6 hospitals was estimated between 74-81% (95% CI 62 – 84%).

Extrapolating these ascertainment data to the entire dataset, overall ascertainment in NLSTEPSS was 74-81% (95% CI 62 – 84%). The ascertainment adjusted estimates of incidence and occurrence of CSE in childhood in North London and England & Wales are presented in Table 5.11. Ascertainment by PHONE was 62 - 68% (95% CI 52 - 70%) and ascertainment by FORMS was 39-43% (95% CI 33 - 44%).

	Frequency of CSE	Rate (per 100,000/yr)	95% CI of Rate (per 100,000/yr)	Ascertainment adjusted Rate (per 100,000/yr)	95% CI of ascertainment adjusted rate (per 100,000/yr)	Ascertainment adjusted N	95% CI Ascertainment adjusted N
North London							
	Incidence	(Crude)14.5	11.5 – 17.6	17.9-19.6	17.3 - 23.4	107 - 118	104 - 141
	Occurrence	(Crude) 25.1	21.1 – 29.1	30.9 – 33.9	29.8 - 40.5	186 - 204	179- 243
England & Wales							
	Age-adjusted incidence	13.2	12.5 – 13.9	16.3 - 17.8	15.7 - 21.3	1710 - 1877	1647 - 2234
	Ethnicity-adjusted incidence	11.5	11.1 - 12.0	14.2 – 15.5	13.7 – 18.5	1489 -1626	1437 - 1940
	Age-adjusted occurrence	25.4	22.5-28.2	31.4 – 34.3	30.2 – 41.0	3293 - 3598	3168 - 4300
	Ethnicity-adjusted occurrence	21.4	20.8-22.0	26.4 – 28.9	25.5 – 34.5	2769 - 3031	2677 - 3619

Table 5.11: Frequency of incidence and occurrence of CSE in childhood in North London and projection for England &Wales.

Age and Ethnicity adjusted incidence and occurrence rates for England and Wales were determined by directly adjusting the North London incidence and occurrence rates to the UK Census 2001 paediatric population of England and Wales. Through three source capture-recapture methods, minimum and maximum estimates of the degree of ascertainment in NLSTEPSS were obtained. Thus, ascertainment adjusted rates are presented as a range of values with the lower values reflecting the rates adjusted using maximum ascertainment estimates. Between 104 and 141 children in North London are estimated to have a lifetime first episode of CSE each year and there are approximately 179 – 243 episodes of CSE in children in North London each year. Extrapolating this data to the paediatric population of England and Wales, and adjusting for age and ethnicity, approximately 2677 – 4300 episodes of CSE will occur in children throughout England and Wales each year.

5.3.14 Aetiology of incident CSE

Prolonged febrile seizures are the most common type of CSE in childhood. Half of children with incident episodes are previously neurologically normal. Only 12% of children with incident CSE have idiopathic or cryptogenic epilepsy. CNS infections are the most common cause of acute symptomatic CSE. For further details on the aetiology of incident episodes of CSE see Figure 5.7

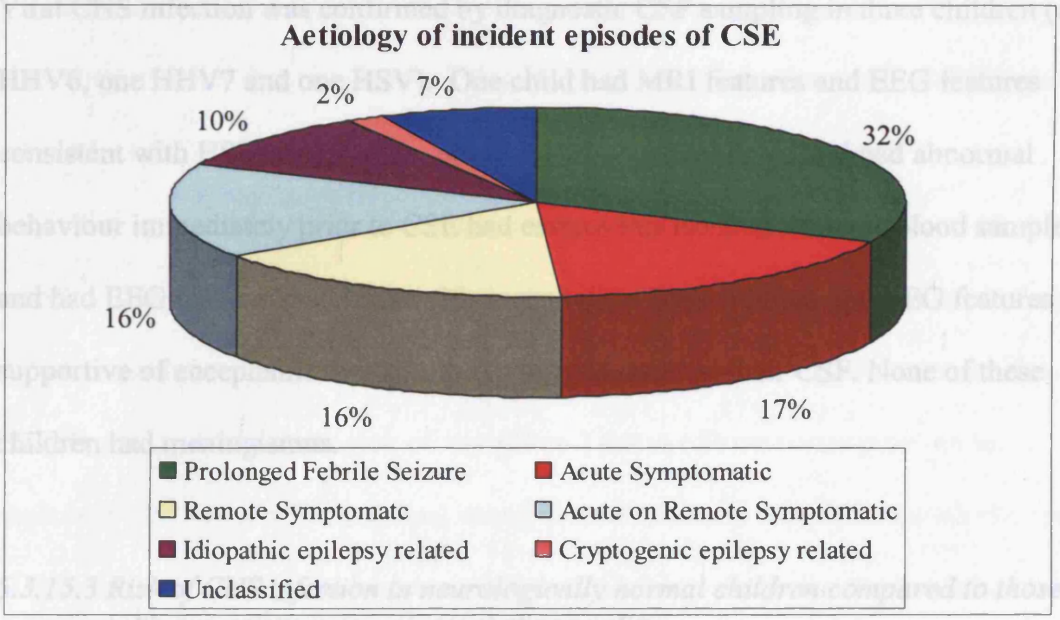

Figure 5.7: Aetiology of Incident episodes of CSE

5.3.15 Population risk of acute bacterial/viral CNS infection in incident episodes of CSE associated with fever

The population risk of acute bacterial/viral CNS infection in children with an incident episode of CSE associated with fever is 19% (95% CI 11– 27%).

5.3.15.1 Risk of Acute Bacterial Meningitis

There were 95 children with incident episodes of CSE associated with fever (above 38^0C on presentation). Of these, 11 (12%, 95% CI 6-18%) children had acute

bacterial meningitis confirmed on diagnostic cerebro-spinal fluid (CSF) sampling (nine *S. pneumoniae,* two *N. meningitides).* The median age of the children (6 male) was 0.6 yrs (range 0.1-3.9 yrs). In none of these children was meningismus reported.

5.3.15.2 Risk of Acute Viral CNS infection

In a further seven (8%, 95% CI 2-13%) children, the final diagnosis was viral CNS infection. The median age of these children (3 male) was 1.2 yrs (range 0.6-8.7). Viral CNS infection was confirmed by diagnostic CSF sampling in three children (one HHV6, one HHV7 and one HSV). One child had MRI features and EEG features consistent with HSV encephalitis, one child who was confused and had abnormal behaviour immediately prior to CSE had enterovirus isolated from his blood sample and had EEG features consistent with encephalitis. Two children had EEG features supportive of encephalitis but no viruses were isolated in their CSF. None of these children had meningismus.

5.3.15.3 Risk of CNS infection in neurologically normal children compared to those with pre-existing neurological abnormality

In a subgroup analysis of the 95 children with incident episodes of CSE associated with fever, 73 were previously neurologically normal and 22 had pre-existing neurological abnormality. Of the 18 children with an acute CNS infection, only one had a previous neurological abnormality; shunted obstructed hydrocephalus due to neonatal intraventricular haemorrhage. Previously neurologically normal children with incident CSE associated with fever are 7.0 (95% CI 0.9 – 55.6) times more likely to have an acute CNS infection compared to children with incident CSE associated with fever but had a pre-existing neurological abnormality.

5.3.16 Outcome of CSE

5.3.16.1 Duration

The mean duration of CSE is 94 mins (median 70 mins, range 30 – 975mins). The median duration of CSE is shorter (Mann-Whitney U-test, p=0.045) if CSE has an out of hospital onset (mean 86 mins, range 30-975 mins) compared to onset in hospital (mean 121 mins, range 30 – 900 mins).

5.3.16.1.1 Factors associated with CSE lasting longer than 60 minutes

Intermittent rather than continuous CSE, longer interval between onset of CSE and arrival in A&E, lack of prehospital treatment and more than 2 doses of benzodiazepines were independently associated with CSE lasting more than 60 minutes. There was no significant interaction between administration of more than 2 doses of benzodiazepines and lack of prehospital treatment i.e. there was no evidence that the effect of administration of more than 2 doses of benzodiazepines on the increased likelihood of CSE lasting longer than 60 minutes was different whether part of that treatment was given prehospital or not. Children that were not treated in the prehospital setting were 2.4 times more likely to have CSE lasting longer than 60 minutes than those that were treated (p=0.028, 95% CI 1.1-5.3). For each minute's delay from onset of CSE to arrival in A&E, the risk of CSE lasting longer than 60 minutes increases by 5% (p=0.003, 95% CI 2-8%). For further details on the factors associated with CSE duration >60 minutes, see Table 5.12.

Variables	*p*	Odds Ratio	95% CI for Odds Ratio	
			Lower	Upper
Intermittent CSE	0.004	3.1	1.4	6.6
Time to AE (mins)	0.003	1.05	1.02	1.08
No Prehospital treatment	0.028	2.4	1.1	5.3
More than 2 doses benzodiazepines	0.001	3.6	1.7	7.9

Table 5.12: Multivariate logistic regression model for factors associated with CSE lasting longer than 60 minutes compared to CSE lasting 30-60 minutes.

5.3.16.2 Recurrence

The one year risk of recurrence following an incident episode of CSE was 17% (n=17, 95% CI= 10-25%). Median age at time of incident episode of CSE was 2.1 years (range 0.4-12.8 years). Seven children had one further episode, seven had two further episodes, two had four further episodes and one child had nine further episodes within one year after incident episode of CSE. The child with nine further episodes of CSE had a focal area of cortical dysplasia. The risk of recurrence is highest (47%), when incident CSE is due to a remote symptomatic aetiology (n=7). Amongst 30 incident episodes of prolonged febrile seizures during the first year of the study, 17% (n=5) had at least one further episode of prolonged febrile seizures within a year of incident CSE. Children with a pre-existing neurological abnormality were 2.8 (95% CI 1.2-6.8, p = 0.041) times more likely to have a recurrence within one year of incident CSE compared to children who were previously neurologically normal.

5.3.16.3 Mortality

During the study period, seven children died during hospitalisation. Of these, six had no previous episode of CSE (M: F = 3:3, median age 1.1yrs, range 0.18 – 5.15yrs).

The other child was male and was aged 13. 4 yrs. Case fatality amongst incident episodes of CSE = 3.4% (95% CI = 2.7 – 4.1%) and in-hospital mortality rate was 5/one million children/yr. Three children had acute bacterial meningitis, one had glutaric aciduria type I and three children (including the child who had a previous episode of CSE) had an undiagnosed progressive neurodegenerative abnormality.

5.4 Discussion

5.4.1 Incidence of CSE in NLSTEPSS compared to other population based studies

5.4.1.1 Introduction

Though there have been six other population based studies on SE, five have been primarily based on adult populations and one was restricted to an adult population. Research in a paediatric population is required for an understanding of the epidemiology of CSE in childhood. This is the first population based study on CSE in that is based on a paediatric population.

The data from this study suggest that the incidence of CSE in childhood in North London is 18-20/100,000 children/yr (95% CI 17 – 23/100,000 children/yr), which contrasts with the range of incidence of SE (4-38/100,000 children/yr) reported in previous population based studies.

5.4.1.2 Effect of differences in study designs and methods

Continuing the arguments on the incidence of SE across adult and childhood age groups in Chapter 2, the lowest previously reported incidence of SE in childhood is very likely to be an underestimate of the true incidence of SE. The lowest incidence

was reported in a California based study that, as in NLSTEPSS, was confined to cases of convulsive status epilepticus (Wu et al. 2002). Cases of CSE were retrospectively identified by a search for specific ICD codes within a database of discharge abstracts for all admissions to non-federal hospitals in California. Errors in hospital discharge coding and the non-inclusion of federal hospitals may have resulted in an underestimate of the true incidence of CSE, a likely possibility acknowledged by the researchers themselves. The study with the highest reported incidence of SE in childhood involved the prospective identification of patients with all forms of SE in hospitals in Richmond, Virginia. However, only 29 children were identified over the 2 year study period (Delorenzo et al. 1996) and therefore the 95% confidence interval of the incidence of SE from that study is wide at 18-57/100,000/yr. The higher incidence of SE in that study by the Richmond Group, compared to other groups, has been attributed to higher ascertainment of cases and to a larger proportion of non-white residents in Richmond; the incidence of SE being higher in non-white people. However, in Chapter 2, the candidate hypothesised that differences in ascertainment may not be the only explanation for the higher incidence of SE reported in the Richmond study. The population based study of SE in Hessen, Germany, had similar ascertainment, similar methodological quality score and included NCSE and CSE as in the Richmond study (Knake et al., 2001). However, the ascertainment adjusted incidence of SE in the Hessen study was a third of that in the Richmond study. The findings from NLSTEPSS support the hypothesis that ascertainment may not be the sole explanation for the higher incidence of SE reported by the Richmond group, as the ascertainment adjusted incidence in NLSTEPSS is still only half of that in the Richmond study. The ascertainment in Richmond was a mean of 60% compared to

74-81% (95% CI 62-84%) in the current study. Thus, the higher incidence in the Richmond study is unlikely to be due to better ascertainment.

5.4.1.3 Effect of differences in ethnic and socioeconomic composition

The current study confirms the observation in other studies that the incidence of CSE in non-white populations is higher than white populations (DeLorenzo et al., 1996; Coeytaux et al., 2001) but in a subgroup analysis of ethnic groups within the NLSTEPSS population, there was no difference in the incidence of CSE amongst black children compared to white children. This is in stark contrast to the three fold difference in the Richmond study. NLSTEPSS is the first study to examine the independent effects of socioeconomic status and ethnicity on the incidence CSE. After taking socioeconomic status into account, Asian children and children of other non-white ethnicity, but not black children, have a significantly higher incidence of CSE compared to white children in NLSTEPSS. Independent of age and ethnicity, there is a particularly strong relationship between the incidence of CSE and socioeconomic status, thereby suggesting that socioeconomic status is a risk factor for developing CSE independently of ethnicity.

Increasing frequency associated with lower socioeconomic status is seen in a range of other conditions such as epilepsy, asthma, diabetes, depression, cancer and meningococcal disease (Acheson et al., 1998; Heaney et al., 2002; Basagana et al., 2004; Feldman et al., 2004; Williams et al., 2004). The precise pathophysiological mechanisms through which socioeconomic status might increase the risk of CSE are not clear but overcrowding, poor nutrition, infections, trauma, birth defects and perinatal complications are also more common in socioeconomically deprived groups.

These socioeconomic risk factors provide plausible explanations for a higher incidence of CSE in those that are less well off. Another factor to be considered is delayed access to medical services, as previous studies have illustrated that families of lower socioeconomic status have delayed access to acute medical care (Weissman et al., 1991; Freeman and Corey 1993; Committee on Pediatric Emergency Medicine 2000; Feinberg et al., 2002). In NLSTEPSS, on univariate linear regression analyses, the intervals between (1) onset of CSE and calling emergency services and (2) calling emergency services and arrival of the ambulance service to the patient, were independent of the socioeconomic status of the patient ($p= 0.4$ and $p=0.8$ respectively). Therefore, delayed access to medical services is an unlikely reason for a higher incidence of CSE in children of lower socioeconomic status. The higher incidence of CSE in Asian children, independent of socioeconomic status hints at the possibility that genetic as well as environmental factors may have a role. Thus, it is possible that the higher incidence of SE observed in the Richmond study attributed to the racial composition of the population (57% black, 38% white) is confounded by the socioeconomic composition of Richmond. Richmond, relative to the other municipal localities of Virginia (Chesterfield, Hanover and Henrico), has the highest percent of children under age 18 living in poverty (32% compared to 4-8% for the other localities of Virginia), the highest percent of female householders with children under age 5 living in poverty and the lowest median household income (http://oncampus.richmond.edu/connect/issues/demographics/moeser-cen2000_files/frame.html).

5.4.1.4 Effect of differences in inclusion criteria amongst studies

The diagnostic criteria of non-convulsive status epilepticus remain controversial and an EEG is required to confirm the diagnosis. The clinical characteristics and management of CSE and NCSE are different (Lacey 1988; Jordan 1994; Treiman 1996) and it may therefore be more useful to investigate the epidemiology of these forms of SE independently rather than pooling them. Widespread EEG facilities in A&E are not available in North London, therefore NLSTEPSS was confined to episodes of CSE. In the Richmond, Rochester and Swiss studies, episodes of NCSE as well as CSE were included but NCSE was not defined. Complex partial status epilepticus, partial status epilepticus, absence status epilepticus and subtle status epilepticus have all been terms used synonymously with NCSE (Drislane 2000; Chang et al., 2001). If these subtypes are excluded in the Richmond, Rochester and Swiss studies, the remaining subcategories of SE may reflect episodes of CSE and the incidence of CSE in childhood from these studies would range between 10-27/100,000/yr (95% CI 8-43/100,000/yr), which is comparable to that estimated in NLSTEPSS. For further details on the estimated incidence of CSE in these studies, see Table 5.13.

Research Group	**Incidence of CSE in childhood (per 100,000/yr)**	**95% CI**
Richmond	27	10.7 – 43.3
Rochester	12.6	8.5 – 16.7
Swiss	10.0	7.5 – 12.4
North London	14.5	11.5 – 17.5

Table 5.13: Estimates and associated 95% CI of the incidence of CSE in childhood in the Richmond, Rochester, Swiss and North London studies.

Estimates for the Richmond, Rochester and Swiss studies were obtained by excluding cases of complex partial/ partial/ absence/ subtle status epilepticus.

5.4.2 Treatment and incidence of CSE

The incidence of CSE (seizure or series of seizures lasting at least thirty minutes) may be affected by treatment of CSE as there is evidence that early treatment of seizures is more likely to result in seizure termination (Knudsen 1979; Sykes and Okonofua 1988). Therefore, it may be hypothesised that in populations in which prehospital treatment is advocated, a proportion of patients with seizures will have seizure termination within thirty minutes of seizure onset and thus, not develop status epilepticus. In North London, the London Ambulance Service has a policy that children with seizures should be given emergency anti-epileptic drug therapy before arrival to hospital (London Ambulance Service 2003). The treatment of CSE in North London will be characterised in the next chapter.

5.4.3 Ascertainment-adjusted incidence of CSE in childhood

Identification of cases using a single source is likely to result in an underestimation of cases and a multi-source identification system may therefore have a better ascertainment (Allison et al., 2003). Identification of cases of CSE through a search of the admission database for relevant ICD codes is simple and convenient, but is prone to possible systematic and non systematic errors in coding resulting in missed cases. Similarly, though the effectiveness of the BPSU has been demonstrated, the ascertainment of cases from the BPSU has been estimated to 45% (Rahi and Dezateux 1999). In NLSTEPSS, the candidate used three sources for identification of cases of CSE and applied three source capture-recapture methodologies to estimate the degree of ascertainment. The advantages and validity of using capture-recapture has been described in detail in Chapter 4. Independently, each source may have

underestimated the number of cases of CSE, but by using this method, the number of cases not identified by any of the three sources may be estimated.

During the first year, 69% of episodes of CSE first enrolled into NLSTEPSS were incident episodes but in the second year, 93% of episodes of CSE first enrolled into the study were incident episodes. These data suggest that in the second year, paediatricians were more likely to notify incident episodes of CSE to NLSTEPSS than non-incident episodes.

The overall completeness of ascertainment in NLSTEPSS is 74-81% (95% CI 62 – 84%). To develop a full picture of the epidemiology of CSE in childhood, complete ascertainment is desirable, but a number of population based studies have illustrated the difficulties with this (Folstein et al., 1987; Hebert et al., 1995; Palli et al., 1998; Calle-Pascual et al., 2001; Knake et al., 2001; Tilling et al., 2001; Roche et al., 2002; Pillaye and Clarke 2003). Ascertainment of cases of congenital cataracts through the British Paediatric Surveillance Scheme was 45% (Rahi and Dezateux 1999), which is similar to the estimated ascertainment of the BPSU-like regional monthly surveillance scheme used in NLSTEPSS. A study on completeness of tuberculosis notification in the United Kingdom estimated ascertainment at 51-62% (Pillaye and Clarke 2003). As discussed previously in Chapter 4, a study on the prevalence of Huntington's disease that used at least 14 distinct sources, including advertising to find cases, ascertainment was 60-75% (Folstein et al., 1987). A study on the incidence of stroke in the UK estimated ascertainment at 88% (Tilling et al., 2001). Amongst population based studies on status epilepticus, mean ascertainment of cases was 60% in the Richmond study (DeLorenzo et al., 1996) and in the study by Knake and colleagues in

Germany, the mean ascertainment was 58% (Knake et al., 2001) . Therefore, ascertainment in NLSTEPSS, though not complete, is high.

Three source capture recapture models (loglinear approach and sample coverage approach) were used rather than a two source model in order to take into account possible dependency between sources. The final estimate of the completeness of ascertainment is therefore a range of values that reflect the best fit models for the loglinear and sample coverage approach rather than a single estimate. There may be some debate over the validity of applying the capture-recapture methodology to a sample (six) of all the hospitals involved in the study and extrapolating the data to the entire population. However, the six hospitals represent a high proportion (43%) of the hospitals in North London and they were randomly chosen, suggesting that the sample is likely to be appropriate for the whole of North London. Thus, the ascertainment-adjusted incidence of CSE in childhood from NLSTEPSS is 18-20/100,000/yr (95% CI 17- 23/100,000/yr).

Taking the results of the current study, put in the context of what is already known about status epilepticus in other population-based studies, it is likely that there is no single true incidence of CSE in childhood and the incidence in populations will vary depending on their socioeconomic and ethnic composition. Studies to identify specific socioeconomic and or genetic factors associated with CSE are required to pinpoint potential targets for primary and secondary prevention of CSE. Until EEG testing of all children with suspected NCSE in A&E is widespread practice, the true incidence of NCSE and SE in general will remain elusive.

5.4.4 Previous neurological status, age and incidence of CSE

The results of the current study, NLSTEPSS, confirms that the highest incidence of CSE in childhood is in those aged less than 5 years (Phillips and Shanahan 1989; DeLorenzo et al., 1996; Shinnar et al., 1997). In NLSTEPSS, when CSE occurred in children aged less than 5 years, they were more likely to have been previously neurologically normal and were most likely to have had a prolonged febrile seizure. However, when CSE occurred outside of this age group i.e. occurred in children aged five years of age or older, there was a four fold greater likelihood that the child had an underlying neurological abnormality, including epilepsy, rather than being previously neurologically normal. Together, these results suggest that a life time first episode of CSE in children aged 5 years or older in a previously neurologically normal child is not common and should raise the suspicion of an underlying neurological abnormality, including epilepsy in such children.

5.4.5 Prolonged febrile seizures and mesial temporal sclerosis

Prolonged febrile seizures make up a significant proportion of SE in childhood accounting for up to a third of SE in children. Only one previous study has reported this sub-group as a distinct category (Hesdorffer et al., 1998), with all other studies that included prolonged febrile seizures, categorised prolonged febrile seizures under acute symptomatic causes in accordance with the ILAE guidelines. The recognition of prolonged febrile seizures as a distinct category is important since there is evidence that suggests that the natural history of febrile seizures may be different from that of other acute symptomatic causes of status epilepticus; mortality is less, intellectual outcome is better and the risk of developing epilepsy is less in subjects with prolonged febrile seizures compared to those with other acute symptomatic SE

(Ellenberg and Nelson 1978; Maytal et al., 1989; Verity and Golding 1991; Verity et al., 1993). There is a longstanding hypothesis that prolonged febrile seizures may cause mesial temporal sclerosis, the most common structural substrate for epilepsy requiring surgical intervention (Cavanagh and Meyer 1956; Abou-Khalil at al. 1993). To date, data from prospective outcome studies of prolonged febrile seizures have been inconclusive about whether prolonged febrile seizures cause mesial temporal sclerosis. Studies of prolonged febrile seizures all report a higher risk of epilepsy in these children compared to the general population. However, they have not specifically addressed whether an increased risk of temporal lobe epilepsy occurs and no imaging data are available on these cohorts. Hence, the incidence of MTS cannot be assessed (Annegers et al., 1987; Verity et al., 1993; Berg and Shinnar 1996). Recent MRI studies have demonstrated abnormalities in the hippocampus consistent with acute changes in the hippocampus within 5 days of prolonged febrile seizures (Scott et al., 2002; Scott et al., 2003). Therefore, children with prolonged febrile seizures are an important group to identify and study and prolonged febrile seizures cannot be considered a completely benign event. Longer term longitudinal MRI studies, are required to further investigate the hypothesis that prolonged febrile seizures may cause mesial temporal sclerosis.

There is accumulating evidence that the likelihood of brain damage following prolonged febrile seizures may have a genetic component. A family history of febrile seizures is a well recognized major risk factor for febrile seizures in offspring (Waruiru and Appleton 2004). A clear genetic component to SE was demonstrated in twin studies by Corey and colleagues (Corey et al., 1998; Corey et al. 2004). The researchers reported a risk of SE of 38% among the co-twins of monozygotic twins

who experienced SE. A polymorphism at the interleukin-1β (IL-1β) locus has been reported in patients with temporal lobe epilepsy with MTS, suggesting that genetic factors may contribute to the development of MTS after a prolonged febrile seizure (Kanemoto et al., 2000; Kanemoto et al., 2003). IL-1β has been implicated in the mechanism of fever generation, in lowering seizure threshold and in prolonging seizures (Crumrine 2002). Despite all these observations suggesting a role for possible genetic factors in the occurrence of prolonged febrile seizures and of seizure-induced injury, little is known about the precise genes involved or the mechanism by which their influence might be exerted. The higher incidence of prolonged febrile seizures in non-white but not black children compared to white children suggest that the search for such candidate genes may be best directed initially at these ethnic groups. The genetic mechanisms involved in the susceptibility to prolonged febrile seizures and the genetic mechanisms responsible for predisposing to seizure-induced injury, offer exciting areas for future research.

5.4.6 Acute bacterial meningitis in children with CSE with fever

Children with CSE and fever are an important subgroup of children with CSE. They include children with prolonged febrile seizures, acute symptomatic CSE due to CNS infections and acute on remote symptomatic CSE. In NLSTEPSS, children with CSE with fever account for half of all incident cases of CSE. Studies of CSE with fever may exclude cases with acute bacterial meningitis to comply with the definition of febrile seizures, but that is a retrospective judgement not appropriate to the emergency management of such cases. Although there are clinical guidelines on the emergency management of the child with CSE (The Advanced Life Support Group 1997; The

Advanced Life Support Group 2000; Appleton et al., 2000) and the child with a first short seizure with fever (American Academy of Pediatrics 1996), there remains uncertainty about the role of parenteral antibiotics, the role of lumbar puncture and the population risk for acute bacterial meningitis in children with CSE with fever.

5.4.6.1 Population risk of acute bacterial meningitis in CSE with fever vs short febrile seizure

Two recently published review articles reported that only 0.4-1.2% of children who have a short seizure associated with fever will have unexpected acute bacterial meningitis (ABM) (Offringa and Moyer 2001; Carroll and Brookfield 2002). Thus, it has been suggested that investigation for ABM is not required in this group, unless other evidence of meningitis is present. However, the data from NLSTEPSS would indicate that the population-risk of acute bacterial meningitis, in children with CSE and fever, is higher than would be expected in a population of children who had short seizures with fever (12% vs 1.2%). Therefore, for management purposes, they should be considered as distinctly different patient populations.

5.4.6.2 The role of antibiotics in children with CSE with fever

The recently published guideline for the management of a child with a seizure recommends antibiotic treatment for children who were drowsy before the seizure, have altered consciousness for more than an hour after seizure, or have meningismus (Armon et al., 2003). None of the patients in this series with proven acute bacterial meningitis had signs of meningismus but these can be subtle in children aged less than a year and most of the children were in that age group. In addition, signs of

meningismus may be attenuated after seizures and or treatment with emergency anti-epileptic drugs. Given the high likelihood of acute bacterial meningitis in patients with CSE with fever, the guideline for use of parenteral antibiotics should be extended to include this population of patients. In addition, from reviews on the treatment and outcome of acute bacterial meningitis, there is evidence that early treatment of acute bacterial meningitis may decrease morbidity and mortality (Aronin et al., 1998; Beaman and Wesselingh 2002; Welch and Nadel 2003).

5.4.6.3 The role of lumbar puncture in children with CSE with fever

The national guidelines for the management of seizures with fever in the United Kingdom issued in 1991 and the "practice parameter" for first simple febrile seizures of the American Academy of Pediatrics (AAP) published in 1996, both recommend lumbar puncture to exclude acute bacterial meningitis in children with short seizures with fever when there are clinical signs of meningitis and strongly recommend lumbar puncture in children under 12 months even in the absence of clinical signs of meningitis (Aicardi et al., 1970; Maytal et al., 1989). Recent publications in *Archives of Disease in Childhood* have contributed to a further debate on the role of lumbar puncture in febrile seizures. Riordan and Cant's review on indications for and contraindications to lumbar puncture concluded that unless there is a specific contraindication, lumbar puncture should be performed if meningitis is suspected (Riordan and Cant 2002). A leading article by Kneen and colleagues, in support of lumbar puncture, highlighted the possible detriment to patient care through declining use of lumbar puncture over the past two decades (Kneen et al., 2002). On the other hand, Carroll and Brookfield challenged the need for lumbar puncture. The authors examined the current guidelines and the available evidence for lumbar puncture

following a short seizure with fever and concluded by advocating fewer lumbar punctures for children with short seizures with fever because of the low risk (1.2%) of acute bacterial meningitis, particularly in the absence of signs of meningitis (Carroll and Brookfield 2002). However, this recommendation relates to children with short seizures with fever and such an approach may not be applicable to children with CSE with fever. Through NLSTEPSS, the candidate has illustrated that acute bacterial meningitis is common in children with CSE with fever and may not be clinically apparent. Thus, the controversy discussed above is of lesser importance in this group of patients.

5.4.6.4 Management strategies for children with CSE with fever

On the basis of the data from the current study, the hypothesises that the most appropriate management for children with CSE with fever is to start parenteral antibiotics early, perform a lumbar puncture when there are no contraindications, base duration and type of therapy on CSF findings and observe closely for potential early complications of acute bacterial meningitis is generated. Several other alternative management strategies may be hypothesised but as each has significant cons (Dodge and Swartz 1965; Rennick et al., 1993; Wylie et al., 1997; Feigin and Pearlman 1998; Pollard et al. 1999; Offringa and Moyer 2001; Riordan and Cant 2002; Armon et al., 2003) they may *not* be appropriate. These include: (1) a period of observation before initiation of treatment; (2) observation and consideration of routine blood investigations for evidence of inflammation; (3) lumbar puncture in the immediate post-ictal period before commencing antibiotics; (4) early intravenous antibiotics but no lumbar puncture

5.4.6.5 Conclusions on acute bacterial meningitis and CSE with fever

The signs for meningismus may be absent in children with CSE with fever due to acute bacterial meningitis. The likelihood of acute bacterial meningitis in children with incident CSE associated with fever estimated from NLSTEPSS is 12%, but this should be considered as a minimum estimate, as lumbar puncture was not universally performed in patients with incident CSE with fever. It is therefore possible that some patients whose episode of CSE was classified as a prolonged febrile seizure may have had a CNS infection. Therefore, there should be a high index of suspicion for acute bacterial meningitis in the child with CSE with fever. Early treatment with parenteral antibiotics, delayed lumbar puncture when there are no contraindications and close observation for signs of raised intracranial pressure may be the most appropriate management.

5.4.7 Seizure characteristics of CSE in childhood

In the current study, focal features were present in 20% of children with prolonged febrile seizures and in 44% of children with acute CNS infection (p= 0.06). These data are consistent with the view that the presence of focal features in a previously neurologically normal, febrile child with CSE should create a suspicion for acute CNS infection. In this cohort of patients, a focal onset of CSE occurred in 36% of incident episodes of CSE but the final seizure type was a generalised seizure in 95% of children. These results are in keeping with the view that a focal onset of CSE is common but most episodes of CSE will secondarily generalise. Similar proportions of children with CSE are likely to have intermittent compared to continuous seizures and clinicians should bear this in mind when assessing seizure termination.

5.4.8 Duration of CSE

The observed median duration of CSE in the population of children in this study is 94 minutes, which is sufficient to increase the potential morbidity and mortality associated with CSE (Dunn 1988; Scholtes, Renier and Meinardi 1996; Logroscino et al., 1997; Waterhouse et al., 1999; Hui et al., 2003). In NLSTEPSS, children who receive prehospital treatment have a reduced seizure length and therefore it is possible that widespread prehospital treatment of seizures that start out of hospital would reduce the likelihood of a 60 minute seizure. It is not within the scope of the study to examine this hypothesis directly as the study excluded children who had seizures lasting less than 30 minutes. However, most seizures that last longer than 5 minutes, are unlikely to stop spontaneously within the next few minutes and will continue for at least 30 minutes unless there has been an appropriate therapeutic intervention (DeLorenzo et al., 1999; Lowenstein et al., 1999; Shinnar et al., 2001a). There are published data that suggest that only a small proportion of children with seizures lasting at least 30 minutes will have spontaneous termination of their seizures (Shinnar et al., 2001a) and the results of NLSTEPSS support this view as only 5 children (3% of incident cases of CSE) in this study did not require treatment for seizure termination. Increasing seizure duration is associated with increasing difficulty in seizure termination and early intervention is therefore indicated (Knudsen 1979; Shinnar et al., 2001a). It may be argued that patients who have a seizure lasting 5 minutes are already likely to have failure of the usual mechanisms of seizure termination and are in the early stages of SE. Thus for treatment purposes, a definition of SE stating a time of 5 minutes may be appropriate (Lowenstein et al., 1999). The patients in NLSTEPSS had seizure activity lasting at least 30 minutes and therefore had seizures that were difficult to terminate. As prehospital treatment

shortens the overall duration of seizures in this group of patients, it is conceivable that prehospital treatment of all seizures that last at least 5 minutes may decrease the ultimate duration of seizure activity. The data from NLSTEPSS also suggest that if prehospital treatment is not available then rapid transport to A&E and earlier intervention, may also reduce the likelihood of seizures lasting longer than 60 minutes and that children that fail to respond to 2 doses of benzodiazepine should be regarded as having CSE refractory to further benzodiazepines and should not receive further doses.

The observed duration of CSE in this cohort of patients is of concern because of the potential associated morbidity and mortality. What is the risk of epilepsy following CSE? What is the risk of temporal lobe epilepsy associated with mesial temporal sclerosis following prolonged febrile seizures? What is the cognitive outcome following CSE? What is the long term mortality associated with CSE? These are all important questions that go beyond the scope of this study, but follow up studies on the cohort of patients in this study may address those questions appropriately.

5.4.9 Recurrence

The data from NLSTEPSS confirm that there is a significant one year risk of recurrence of CSE, including prolonged febrile seizures, particularly when there is an underlying remote symptomatic aetiology. Other studies have reported similar recurrence rates of CSE (DeLorenzo et al., 1996; Hesdorffer et al., 1998; Knake et al., 2001). The risk of recurrence has profound consequences in view of animal and experimental data showing that seizures in early life predisposes the developing brain to more damaging effects from further seizures later in life, and that factors such as

the presence of prior neurological abnormalities, aetiology of the seizures, recurrent seizures and genetic predisposition may affect the range and severity of changes in the brain substrate (Maher and McLachlan 1995; Germano and Sperber 1997; Corey et al., 1998; Dube et al., 1998; VanLandingham et al., 1998; Kanemoto et al., 2000).

5.4.10 Mortality

The 3% mortality associated with CSE observed in NLSTEPSS is similar to the results of other recent studies (Celesia 1983; Maytal et al., 1989; Hauser 1990; Wu et al., 2002). Thus, the short term mortality associated with CSE is lower than the 11% reported in the earlier landmark study of Aicardi and Chevrie (Aicardi et al., 1970) but remains significant. In addition, the data from NLSTEPSS is consistent with that of other studies that aetiology of CSE is a major factor that influences the short term mortality (Maytal et al., 1989; Logroscino et al., 1997; DeLorenzo et al., 1999; Garzon et al., 2003). All the children in NLSTEPSS who died had either acute or remote symptomatic CSE. In a primarily adult based population, Logroscino and colleagues found that short term mortality was highest for *acute symptomatic SE* which accounted for 90% of deaths (Logroscino et al., 1997). In a later study, the same group of researchers found that long term mortality was highest in those patients who had *remote progressive symptomatic* abnormalities such as pre-existing brain tumours or degenerative abnormalities (Logroscino et al., 2002). What this study provides is that in children, *acute or remote symptomatic CSE*, in similar proportions, are associated with the highest short term mortality.

5.4.11 Discussion summary

In summary, the data reported from the current study, NLSTEPSS, show that CSE in childhood is not uncommon and is higher in children that are socioeconomically deprived, in Asian and other non-white, but not black, children compared to white children and in children aged less than 5 years. The data also suggest that children aged 5 years and older with incident episodes of CSE should be investigated carefully for possible underlying neurological abnormalities, including epilepsy. Prolonged febrile seizures are the most common cause of incident episodes of CSE in childhood but it is a diagnosis of exclusion. As the risk of acute CNS infection in children with an incident episode of CSE associated with fever is at least 12%, there should be a high index of suspicion for acute CNS infections in such patients. The corollary of that finding is that there should be a low threshold for empirical treatment for acute CNS infections and close monitoring for raised intracranial pressure in children with an incident episode of CSE with fever. One in every six children with an incident episode of CSE will have a further episode of CSE within a year of the initial episode and there remains a significant risk of death (three per hundred) associated with incident episodes of CSE in childhood. Emergency anti-epileptic drug treatment may improve the outcome of CSE by decreasing seizure duration. In the next chapter, the emergency treatment of CSE in children from NLSTEPSS is characterised.

CHAPTER 6: TREATMENT OF CSE IN CHILDHOOD

6.1 Introduction

The outcome of CSE may also be influenced by treatment through its effect on seizure duration, but there is limited published data on the treatment of CSE in childhood. Consequently, treatment guidelines for the emergency treatment of CSE are based on clinical experience and sparse evidence (Appleton et al. 2000; The Advanced Life Support Group 2000). The provision of standardised guidelines for the treatment of CSE, similar to treating cardiac arrest, is associated with improved quality of emergency care and outcome (Shepherd 1994), but provision of such a guideline does not guarantee that it will be adhered to (Begg 1992; Meyer et al., 1997; Belfer et al., 2001; Levenson 2001; Puder and Keller 2003; Gilbert et al., 2003; Chiang et al., 2004; Johansson et al., 2004). In the United Kingdom (UK), the Advanced Paediatric Life Support (APLS) guideline for the management of CSE is the widely accepted national standard for treatment of CSE but there is ambiguity in that guideline with respect to whether prehospital treatment should be administered and if it is administered, whether A&E physicians should count the administered doses of benzodiazepines as part of the recommended two doses. In the systematic review of the epidemiology of status epilepticus described in Chapter 2, two of the studies reported that a significant proportion of patients were not treated, or inadequately treated, prior to arrival to hospital. Together, these data lead to the hypotheses that in the general childhood population (1) a significant proportion of children with CSE are not treated in the prehospital setting (2) prehospital treatment may decrease the duration of CSE (3) and that physicians who disregard prehospital treatment may give more doses of benzodiazepine than those who take prehospital treatment into account.

Benzodiazepines are the preferred first line drugs for the treatment of CSE because they have a quick onset of action and are effective (Lowenstein and Alldredge 1998; Treiman 1998), but there is a risk of respiratory depression associated with their use which is increased when more than 2 doses are administered (Dieckmann 1994; Norris et al., 1999; Rainbow et al., 2002; Stewart et al., 2002).

In sheep, CSE is associated with centrally mediated respiratory depression (Johnston et al., 1995) and central apnoea has been reported in a case report of near sudden unexplained death in epilepsy (So et al., 2000). In a study on admissions to a paediatric intensive care unit for status epilepticus, 13% of the children required admission because of respiratory depression but a number of these children had not been treated with benzodiazepines (Lacroix et al., 1994). Therefore, respiratory depression is not uncommon with status epilepticus and may be a consequence of treatment, of the seizure itself or of some other factor(s). Identification of factors associated with respiratory depression in convulsive status epilepticus may assist in the development of strategies to minimise the risk of respiratory depression in status epilepticus.

The APLS recommended first line AEDs are lorazepam administered intravenously or diazepam administered rectally but there is no previous study that has examined the effectiveness and safety of these agents administered by these routes. Paediatric studies comparing lorazepam to diazepam in the treatment of convulsive status epilepticus show that children treated with intravenous lorazepam were less likely to require additional doses or an additional AED for seizure termination and were also more less likely to develop respiratory depression than children treated with

intravenous diazepam (Giang and McBride 1988; Chiulli et al., 1991; Appleton et al., 1995). There are data from paediatric studies that also suggest that treatment of convulsive status epilepticus with rectal diazepam is as efficacious, without an increased risk of respiratory depression, as treatment with intravenous diazepam (Knudsen 1979; Albano et al., 1989; Dieckmann 1994; Alldredge et al., 1995). Therefore, as intravenous lorazepam is better than intravenous diazepam, and that rectal diazepam is as efficacious as intravenous diazepam, this leads to the leads to the hypothesis that intravenous lorazepam may be better first line therapy than rectal diazepam for the treatment of convulsive status epilepticus in childhood.

The APLS guideline recommends rectal paraldehyde as the second line agent for the treatment of convulsive status epilepticus following initial treatment with benzodiazepines. Rectal administration of drugs may result in inadequate therapeutic brain levels and it may be more appropriate to administer an intravenous drug if intravenous access is available. Intravenous phenytoin is a widely used second line agent (Scott and Neville 1999). There are no published data on the likelihood of seizure termination with rectal paraldehyde compared to intravenous phenytoin as second line treatment for convulsive status epilepticus in childhood.

Although the results of randomised controlled trials are generally considered as "best evidence", in some situations only observational studies may be conducted. Due to difficulties with consent, randomised controlled trials on the treatment of CSE in children are rare. In the absence of randomised controlled trials, non-interventional studies, such as the current study, may provide the best level of evidence and thus provide important data on the optimum treatment of CSE. From NLSTEPSS the

treatment of convulsive status epilepticus of out of hospital onset is described with particular attention to the following questions:

- What proportion of children with convulsive status epilepticus of out of hospital onset are not treated in the prehospital setting?
- In the general childhood population, what are the factors associated with respiratory depression in convulsive status epilepticus?
- In the general childhood population, are children with CSE being treated with inadequate doses/ more doses to those recommended in the APLS guideline for the emergency management of CSE?
- As first line treatment of convulsive status epilepticus, is intravenous lorazepam associated with a greater likelihood of seizure termination and a lesser risk of respiratory depression than treatment with rectal diazepam?
- As second line treatment of convulsive status epilepticus, is intravenous phenytoin associated with a greater likelihood of seizure termination than rectal paraldehyde?

6.2 Methods

6.2.1 Case ascertainment, data collection and data validation

The methods for case ascertainment, data collection and data validation were described in Chapter 4.

6.2.2 Definitions

6.2.2.1 APLS recommended first line AED

As the APLS guideline is considered the national guideline for the emergency treatment of CSE in childhood, the emergency management of CSE in this study population was compared to the APLS guideline current during the study period i.e. the third edition (The Advanced Life Support Group 2000). In APLS, 3rd Ed, lorazepam (administered intravenously) or diazepam (administered rectally) is the recommended first line drug.

6.2.2.2 APLS recommended second line AED

Paraldehyde (administered rectally) is the recommended second line drug (see Figure 6.1 for further details on the APLS guideline for the treatment of CSE, 3rd Edition).

6.2.2.3 Adequate doses for emergency AEDs

An adequate dose for intravenous (iv) lorazepam is defined as 0.1mg/kg, for rectal (pr) diazepam it is 0.5mg/kg, for pr paraldehyde it is 0.4ml/kg, for iv phenytoin it is 18mg/kg and for iv phenobarbitone it is 15-20mg/kg (see Figure 6.1). The weight used for calculating adequate doses was that estimated by emergency medical personnel. To allow for any errors in estimating the adequate dose of emergency AED, any administered dose outside 80%-120% of these doses, were considered to be inadequate (low) or high.

6.2.2.4 Response to AED

Positive response to an AED was defined as termination of overt clinical seizure activity within 10 minutes of administration of the AED.

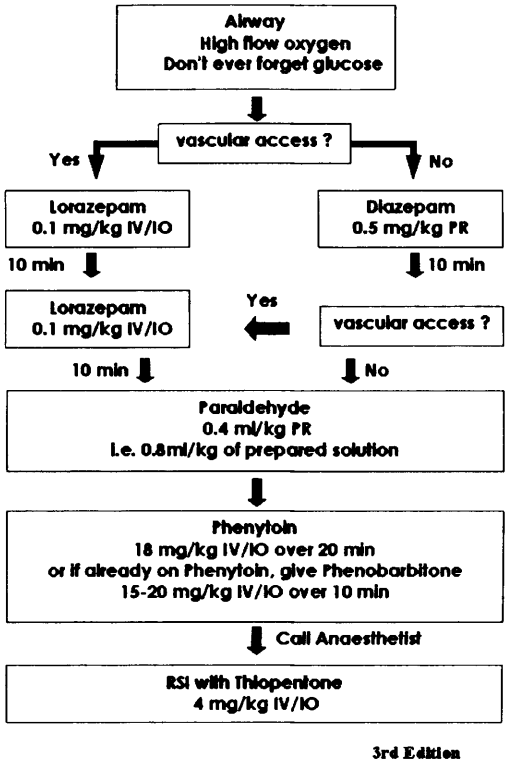

Figure 6.1: APLS algorithm (3rd ed.) for treatment of convulsive status epilepticus.

6.2.2.5 Reasons for admission to PICU

Primary reasons for admission to PICU were classified into one of the following categories: for continuing overt clinical seizure activity, for respiratory depression following cessation of clinical seizure activity, for altered consciousness (Glasgow Coma Scale less than 8), for safety of transfer to PICU and for other reasons.

6.2.3 Statistics

Data analysis was conducted in SPSS Version 10 (Chicago, Illinois) and StatXact v4.0.1. Only first episodes of all children who had CSE during the study period were included in analyses on factors associated with treatment with more than 2 doses of

benzodiazepines, factors associated with respiratory depression and differences in outcome between groups of children treated with different first and second line AEDs.

Forward stepwise multivariate logistic regression was used to investigate factors associated with respiratory depression and factors that may affect the likelihood of being treated with more than 2 doses of benzodiazepines rather than 1 or 2 doses. The critical level for entering and removing variables was set at $p=0.05$ and $p=0.1$ respectively. The following variables were investigated: age, ethnicity, sex, neurological state prior to episode of CSE, interval between onset of CSE and arrival to A&E, incident vs non-incident CSE, onset in hospital or onset out of hospital, CSE associated with fever or not, intermittent versus continuous CSE, presence of focal features or not, prehospital treatment or not, treatment with first AED within 10 minutes of onset of CSE, treatment with first AED within 15 minutes of onset of CSE, adequacy of dose of first AED, treatment with more than 2 doses of benzodiazepines than 1 or two doses and duration of CSE greater than 60 minutes compared to 30 – 60 minutes.

Chi square, Fishers exact and Mann-Whitney U-testing were carried out to examine the differences in seizure and patient characteristics amongst children treated with intravenous lorazepam or rectal diazepam as first line AED, and differences in seizure and patient characteristics amongst children treated with intravenous phenytoin or rectal paraldehyde as second line AED. Differences in seizure termination and risk of respiratory depression between treatment groups were investigated using StatXact v4.0.1. The 95% confidence intervals for the differences in proportions between groups and associated p-values are presented.

6.3 Results

6.3.1 Seizure termination without treatment

There were 240 CSE events of out of hospital onset. Of these, 5 (3 males, median age 6.3 yrs, range 0.65-8.02 yrs) spontaneously terminated. All five children had incident, intermittent episodes of CSE (median duration 61 mins, range 60-80 mins) and were brought to hospital by ambulance (median interval between onset and arrival to hospital 64.5 mins, range 30- 110 mins). One child had prolonged febrile seizures, one had acute bacterial meningitis, one had idiopathic epilepsy related CSE and two had remote symptomatic CSE.

6.3.2 First Line treatment of CSE

6.3.2.1 Initial treatment commenced prehospital

Of the 235 episodes of CSE of out of hospital that required treatment for seizure termination, 131 (56%) were incident and 104 were non-incident cases. Prehospital treatment was less likely to be administered in incident cases of CSE compared to non incident cases (63/131 vs 87/104, 95% CI 23.3 – 47.9%, $p = 0.002$). Three children with CSE were given their first treatment at school but in all other cases of CSE, initial treatment was administered by the child's parents at home or by paramedics. A greater proportion of children with incident episodes of CSE were treated initially by paramedics (50/63) compared to children with non-incident cases of CSE who were more likely to be treated initially by their parents at home (64/84), $p < 0.0005$). Rectal diazepam was the first anti-epileptic medication administered in 96% of all cases treated in the prehospital setting but the dose was adequate in only 21% of cases and the dose was inadequate in 66% of cases (see Table 6.1). Adequacy of the first

dose of prehospital treatment was independent of whether CSE was incident CSE or not (16/63 vs 14/84 respectively, 95% CI - 26.2 – 6.6%, p = 0.31).

Step	AED	Dose	Prehospital N (%)	Overall (prehospital and hospital) N (%)
FIRST LINE				
Treated			147 (63)	235 (100)
	Diazepam			
		Dose low	93 (66)	125 (66)
		Dose adequate	29 (21)	45 (24)
		Dose high	4 (3)	5 (3)
		Dose unknown	15 (11)	14 (7)
		Total	141 (96)	189 (80)
	Lorazepam			
		Dose low	-	3 (8)
		Dose adequate	-	32 (89)
		Dose high	-	1 (3)
		Dose unknown	-	0 (0)
		Total	-	36 (15)
	Other		6 (4)	10 (4)
SECOND LINE				
Treated				79 (34)
	Paraldehyde			
		Dose low	-	11 (26)
		Dose adequate	-	31 (72)
		Dose high	-	1 (2)
		Dose unknown	-	0 (0)
		Total	-	43 (54)
	Phenytoin			
		Dose low	-	3 (9)
		Dose adequate	-	29 (91)
		Dose high	-	0 (0)
		Dose unknown	-	0 (0)
		Total	-	32 (41)
	Phenobarbitone			
		Dose low	-	3 (75)
		Dose adequate	-	1 (25)
		Dose high	-	0 (0)
		Dose unknown	-	0 (0)
		Total	-	4 (5)

Table 6.1: Details of choice of first line and second line AEDs and adequacy of their doses in the treatment of CSE of out of hospital onset in children in North London (n=235).

The median interval between seizure onset and to call the emergency services was 7 minutes (range 0 to 495 minutes), the median interval between calling emergency services and arrival of a paramedics to the child was 11 minutes (range 5 to 19 minutes) and the median interval from onset to administration of the first prehospital dose of AED was 11 mins (5 minutes if administered by parents at home, 20 minutes if administered by paramedics, range 0-460 mins). The median interval between onset and arrival to A&E was 36 mins (range 5-509 mins).

6.3.2.2 Initial treatment in A&E

In those 88 CSE events that were not treated in the prehospital setting, 64 (73%) were taken to hospital by ambulance. The median interval between onset and arrival to A&E overall was 34 mins (range 5-514 mins) and 39 mins (range 10 -514) if brought by ambulance. Similar proportions of children who were not treated before arrival to hospital were treated with rectal diazepam (55%) and intravenous lorazepam (41%) as the first line AED in hospital. Those that were treated with intravenous lorazepam were 16 (95% CI 4.8-53.1%, p = 0.02) times more likely to receive an adequate dose compared to those that received rectal diazepam.

6.3.2.3 Rectal diazepam or intravenous lorazepam as first line AED

6.3.2.3.1 Prehospital treatment given

In children with CSE of out of hospital onset and treated with a *single* dose of rectal diazepam before arrival to A&E and then given a second dose of benzodiazepine in A&E, similar proportions responded to the second dose (had seizure termination) with intravenous lorazepam as those treated with rectal diazepam (14/46 vs 7/26, 95% CI for difference -29.3 to 20.5%, p = 0.78). Of the 21 children who responded to the

second dose of benzodiazepine, 16 were treated with an inadequate first dose and 5 were treated with an adequate first dose in the prehospital setting. The likelihood of seizure termination was similar whether the second dose was adequate or not (p=0.9). The median age, male to female ratio, median interval between onset and arrival to accident and emergency, proportion of episodes that were intermittent compared to continuous and the proportion of episodes that were prolonged febrile seizures were similar between groups. Children who were treated with rectal diazepam as the second dose of benzodiazepine were more likely to have had CSE with focal features and non-incident CSE compared to those who were treated with intravenous lorazepam. For further details on clinical characteristics according to treatment group, see Table 6.2.

6.3.2.3.2 No prehospital treatment given

In children with CSE of out of hospital setting and *not* treated in the prehospital setting, initial treatment with intravenous lorazepam was associated with a greater likelihood of seizure termination compared to those given rectal diazepam (16/36 vs 6/50 respectively, 95% CI for difference, 11.0 – 53.9%, p= 0.005) without an increased risk of respiratory depression (7/36 vs 8/50, 95% CI for difference -16.7 – 27.3%, p= 0.79. However, those that were treated with intravenous lorazepam were more likely to be treated with an adequate dose of AED (32/36 vs 13/50, 95% CI for difference 43.4 – 78.9%, p=0.002). An adequate first dose of AED and intravenous lorazepam rather than rectal diazepam as initial treatment were variables significantly associated with seizure termination on univariate logistic regression, but were not independently significant on multivariate analysis. The mean interval between onset and arrival to A&E was greater in the group of children treated with intravenous

lorazepam compared to those treated with rectal diazepam (67 vs 47 mins, Mann-Whitney U-test, p = 0.04) but the median age, male:female ratio and other seizure and patient characteristics were similar in both groups. For further details on clinical characteristics according to the two treatment groups, see Table 6.3.

	Diazepam (%)	Lorazepam (%)	Total (%)
Age (yrs)			
Mean	3.9	4.8	
Median	3.3	3.4	-
Range	0.3 -11.1	0.7 – 15.9	-
Mann-Whitney U-test, p =0.5			
Sex			
Male	12 (46)	17 (37)	29 (38)
Female	14 (54)	29 (63)	43 (62)
Chi-square =0.6, df = 1, p = 0.44			
Time to A&E(mins)			
Mean	55	36	-
Median	32	31	
Range	10 - 492	10 – 94	-
Mann-Whitney U-test, p =0.5			
Character			
Intermittent	11 (42)	18 (39)	29 (41)
Continuous	15 (58)	28 (61)	43 (59)
Chi-square =0.07 , df = 1, p =0.8			
Aetiology			
PFS	4 (15)	9 (20)	13 (18)
Not PFS	22 (85)	37 (80)	59 (82)
Fishers Exact Test Chi-square = 0.20, df = 1, p = 0.65			
Seizure type			
Focal	16 (62)	15 (33)	31 (43)
Generalised	10 (38)	31 (67)	41 (54)
Chi-square = 5.7, df = 1, p =0.017			
Incident/Non-Incident			
Incident	6 (23)	28 (61)	34 (47)
Non-Incident	20 (77)	18 (39)	38 (53)
Chi-square = 9.5., df = 1, p =0.002			
All	26 (100)	46 (100)	72 (100)

Table 6.2: Patients' characteristics and their seizure characteristics according to the first benzodiazepine given in hospital after initial treatment with single dose of rectal diazepam in the prehospital setting.

	Diazepam (%)	Lorazepam (%)	Total (%)
Age (yrs)			
Mean	3.6	3.8	
Median	2.1	2.1	-
Range	0.16 – 15.5	0.32 – 13.3	-
Mann-Whitney U-test, p = 0.44			
Sex			
Male	26 (52)	22 (61)	48 (56)
Female	24 (48)	14 (39)	38 (44)
Chi-square = 0.71, p =0.4			
Time to A&E(mins)			
Mean	47	67	
Median	30	42	-
Range	5 - 514	10- 450	-
Mann-Whitney U-test, p = 0.04			
Character			
Intermittent	25 (50)	19 (53)	42 (49)
Continuous	25 (50)	17 (47	44 (51)
Chi-square = 0.71, p =0.40			
Aetiology			
PFS	32 (64)	26 (72)	58 (67)
Not PFS	18 (36)	10 (28)	28 (33)
Chi-square = 0.64, p =0.42			
Seizure type			
Focal	16 (68)	27 (75)	61 (71)
Generalised	34 (32)	9 (25)	25 (29)
Chi-square = 0.50, df = 1, p = 0.48			
Incident/Non-Incident			
Incident	39 (78)	30 (83)	69 (80)
Non-Incident	11 (22)	6 (17)	17 (20)
Chi-square = 0.37, df = 1, p = 0.54			
ALL	50 (100)	36 (100)	86 (100)

Table 6.3: Patients' characteristics and their seizure characteristics according to the first benzodiazepine given in hospital when there was no prehospital treatment.

6.3.3 Second Line Treatment of CSE

6.3.3.1 Choice of AED and adequacy of dose

Second line AED was administered in 79 (34%) children. Rectal paraldehyde (54%) and intravenous phenytoin (41%) were the preferred second line AEDs and when used, their dose was frequently adequate. Similar proportions of children treated with rectal paraldehyde or intravenous phenytoin were given adequate doses. For further details on the first and second line choice of AEDs and adequacy of doses, please see Table 6.1.

6.3.3.2 Rectal paraldehyde or intravenous phenytoin as second line AED

In children with CSE of out of hospital setting and who required second line AED therapy, 75 were treated with either rectal paraldehyde or intravenous phenytoin as second line treatment. Second line treatment with intravenous phenytoin was associated with a greater likelihood of seizure termination than treatment with rectal paraldehyde (26/32 vs 12/43 respectively, 95% CI for difference 31.8-72.87%, p=0.02). Similar proportions of children were treated with adequate doses (29/32 vs 31/43, 95% CI for difference -42.5 to 3.2%, p = 0.11) and similar proportions of children were treated with more than 2 doses of benzodiazepines compared to treatment with 1 or 2 doses (20/32 vs 23/43, 95% CI for difference -42.5 to 3.2%, p = 0.82). The median age, male to female ratio, mean interval between onset of CSE and arrival to the accident and emergency department, proportion of episodes that were intermittent compared to continuous, and the proportion of episodes that were prolonged febrile seizures were also similar between treatment groups. For further details of clinical characteristics according to treatment group, see Table 6.4.

	Paraldehyde (%)	Phenytoin (%)	Total (%)
Age (yrs)			
Mean	3.4	3.5	
Median	2.2	2.0	
Range	0.3 - 15.3	0.2 - 15.9	
Mann-Whitney U-test, p = 0.11			
Sex			
Male	22 (51)	22 (68)	44 (59)
Female	21 (49)	10 (32)	31 (41)
Chi-square = 2.1, p =0.15			
Time to A&E(mins)			
Mean	51	60	
Median	34	45	
Range	10 - 240	10-514	
Mann-Whitney U-test, p = 0.69			
Character			
Intermittent	20 (47)	16 (50)	36 (48)
Continuous	23 (53)	16 (50)	39 (52)
Chi-square = 0.06, p =0.80			
Aetiology			
PFS	9 (22)	8 (25)	17 (23)
Not PFS	34 (79)	24 (75)	58 (70)
Chi-square = 0.12, p =0.73			
Seizure type			
Focal	14 (33)	9 (28)	23 (31)
Generalised	29 (67)	23 (72)	52 (69)
Chi-square = 0.19, p =0.66			
Incident/Non-Incident			
Incident	37 (86)	30 (93)	67 (89)
Non-Incident	6 (14)	2 (7)	8 (11)
Fishers Exact Test, p = 0.48			
Doses of Benzodiazepines administered			
1 or 2 doses	20 (47)	12 (37)	32 (43)
>2 doses	23 (53)	20 (63)	43 (57)
Chi-square = 0.95, p =0.33			

Table 6.4: Patients' characteristics and their seizure characteristics according to the choice of second line emergency AED.

6.3.4 Respiratory depression and CSE

Of the 226 children with initial episodes of CSE, all 36 (16%) children that developed respiratory depression required admission to PICU. The children treated with more than 2 doses of benzodiazepines were more likely to have respiratory depression than those treated with 1 or 2 doses (20/89 vs 16/131, chi square = 4.07, $p = 0.044$). Treatment with more than 2 doses of benzodiazepines rather than 1 or 2 doses was the sole significant factor on multivariate logistic regression analysis of possible factors of CSE associated with respiratory depression. Of note, on univariate logistic regression, adequacy of the initial dose of benzodiazepine administered was not associated with respiratory depression (p= 0.36).

6.3.5 Factors associated with treatment with more than two doses of benzodiazepines

Half the number of children that required treatment for termination of CSE were treated with more than the maximum two doses of benzodiazepines recommended in the APLS guideline. On multivariate logistic regression the following variables were independently associated with treatment with more than 2 doses of benzodiazepines: prehospital treatment vs no prehospital treatment, inadequate vs adequate first dose of AED, CSE lasting >60 mins rather than CSE lasting 30-60 mins, and admission to PICU. There is a significant interaction effect between prehospital treatment and inadequate vs adequate dose of the first AED. An adequate first dose was associated with an 11.4 fold increase in the likelihood of being treated with more than 2 doses of benzodiazepines (p< 0.0005, 95% CI 3.8-34.5) when given in the pre hospital setting. However, if the first dose was inadequate, the likelihood of having more than 2 doses of benzodiazepine increased by a similar amount regardless of whether it was given in

hospital (3.4-fold), or prehospital (3.1-fold). For further details on factors associated with treatment with more than two doses of benzodiazepines, see Table 6.5.

Variables	*p*	Odds Ratio	95% CI for Odds Ratio	
			Lower	Upper
Duration > 60 mins	0.007	2.2	1.3	3.9
Prehospital treatment with an adequate dose of first AED vs no prehospital treatment	<0.0005	11.4	3.8	34.5
Prehospital treatment with inadequate dose of first AED vs no prehospital treatment	<0.0005	3.1	0.78	11.6
Inadequate vs Adequate dose of first AED overall	<0.0005	3.4	1.1	10.2
Admission to PICU	0.02	2.1	1.1	3.9

Table 6.5: Multivariate logistic regression of factors associated with treatment of CSE with more than 2 doses of benzodiazepines rather than one or two doses.

6.4 Discussion

In NLSTEPSS, 37% of children with CSE of out of hospital onset are not treated in the prehospital setting. This is significant as the data from the previous chapter show that lack of prehospital treatment is associated with increased likelihood of CSE lasting longer than 60 minutes than 30-60 minutes and previous studies have reported increasing morbidity and mortality associated with increasing duration of CSE. The data from Chapter 5 also show that treatment with more than two doses of benzodiazepines is associated with an increased likelihood of CSE lasting longer than 60 minutes than 30 to 60 minutes.

In the current study, treatment with more than two doses of benzodiazepines is not only associated with increased seizure length, it is also associated with the development of respiratory depression. The development of respiratory depression associated with treatment with more than two doses of benzodiazepines has been reported previously (Stewart et al., 2002). Following an initial dose, subsequent treatment with at least two more doses of benzodiazepines may result in high serum levels with resultant respiratory depression; the higher the initial dose, the higher the serum level. However, in the current study, adequacy of the initial dose of benzodiazepines was not associated with the development of respiratory depression. The most likely explanation for this unexpected finding is that the study had insufficient power. Alternatively, children who do not respond to an adequate initial dose of AED are more likely to have refractory CSE and respiratory depression occurs as a result of seizure activity rather than treatment.

In the current series, prehospital treatment is associated with administration of more than 2 doses of benzodiazepine. Children treated with an adequate initial dose are more likely to be treated with more than two doses of benzodiazepines than those treated with an inadequate initial dose. The associations between treatment with more than two doses of benzodiazepines, increased seizure length and respiratory depression have already been described in the current study. Several factors may contribute to these observations. The first is that physicians who disregard prehospital treatment may give more than the maximum two doses of benzodiazepine in the APLS guideline than those who do take prehospital treatment into account. This may be due to a lack of specificity of the entry point into the treatment algorithm of the

APLS guideline. The issue becomes more ambiguous because the British Paediatric Neurology Association (BPNA) guideline for treatment of CSE recommends that prehospital treatment should be ignored (Appleton et al. 2000) which, on the basis of the current data, may increase the risk of respiratory depression and contribute to increased seizure duration. Thus, the entry point into the guidelines for the management of CSE needs to be clarified. It may also be hypothesised that children who do not respond to an adequate initial prehospital dose of AED, and ultimately have seizure activity lasting at least thirty minutes, are more likely to have refractory CSE compared to those who were inadequately or not treated. Conversely, children inadequately treated in the prehospital setting are likely to respond to treatment in the hospital setting, suggesting that seizure duration would have been shorter in a significant proportion of children if the initial dose were adequate. In NLSTEPSS, 22% of children who were given a single inadequate initial dose of benzodiazepine in the prehospital setting had seizure termination after a second dose of a benzodiazepine in hospital. It is therefore possible that this 22% of children may have had shorter seizure duration had they been given an adequate initial dose. If this hypothesis is true, an adequate initial prehospital dose of AED may be important in the management of convulsive status epilepticus.

On this basis, the current state of treatment of childhood CSE is worrying as only one in twelve children with CSE of out of hospital onset are treated with an adequate first dose of prehospital treatment, and four in ten children are treated with more than two doses of benzodiazepines. It would appear that parents are aware of the importance of early treatment of CSE since non-incident episodes of CSE are more likely to be treated initially by parents rather than by paramedics, but the doses they give are

frequently inadequate. Administration of an inadequate dose is also common when initial treatment is administered by paramedics. Half of children with incident episodes of CSE have no previous neurological abnormality so it is not surprising that if prehospital treatment is given to children with incident episodes of CSE, it is usually administered by paramedics. Though 83% of incident episodes of CSE are transported to hospital by ambulance, only half of these children will receive prehospital treatment, of which only a quarter will get an adequate first dose. Thus, only one in ten children with incident CSE and transported to A&E by ambulance will get an adequate first dose of prehospital treatment. The reason(s) for not giving any or inadequate prehospital treatment is unclear and should be investigated, but differences in the APLS guideline for the treatment of CSE compared to that used by the London Ambulance Service and staffing levels of paramedics may contribute significantly to problems with prehospital treatment.

The APLS guideline recommended dose of rectal diazepam of 0.5mg/kg is consistent with the pharmacokinetics of the drug. In pharmacokinetic studies of rectal diazepam in children, 0.4 – 0.5 mg/kg is required to attain therapeutic anti-epileptic serum levels within ten minutes of administration (Mattila et al., 1981; Ogutu et al., 2002). In the London Ambulance Service's guideline, diazepam by the intravenous route or rectal route is recommended but the use of intravenous therapy is limited by the difficulty in achieving intravenous access in children particularly in those aged less than 5 years, the peak age group for convulsive status epilepticus in childhood. No child in this study was given intravenous therapy by paramedics. The dose of rectal diazepam recommended in the London Ambulance Service's guideline is based on the child's age rather than weight (2.5 mg for children aged less than 1 year, 5 mg for those aged

1-5 years and 10 mg for those aged 6-12 years) (London Ambulance Service 2003), but the data from the current study suggest they are not compliant with their own guideline. Sixty percent of the children aged 1-5 years in the current study treated by paramedics were treated with 2.5 mg rather than 5 mg as recommended in the LAS guideline. Even if the LAS guideline had been strictly adhered to, a proportion of children would still not have received an adequate per kilogram dose to achieve therapeutic anti-epileptic levels. Rectal diazepam is only available in prepackaged, set doses, making it difficult to accurately vary the dose according to the patient's weight and therefore, may contribute to difficulty with administration of an adequate first dose. Furthermore, paramedics are not always dispatched to 999 calls related to children with seizures. The London Ambulance Service considers CSE in childhood as a Category A emergency i.e. immediately life-threatening condition and as a policy, attempts to dispatch a paramedic trained to administer emergency rectal diazepam for such calls (London Ambulance Service 2004). However, if a paramedic is not immediately available, ambulance technicians are dispatched to transport the child to hospital for initiation of treatment as soon as possible (Wright 2005). In the current study, the median time to be transported to A&E by ambulance from the onset of CSE was 39 minutes, which is long enough to increase the difficulty with seizure termination and mortality associated with CSE (Knudsen 1979; Hui et al., 2003). Therefore, strategies to improve prehospital treatment of CSE by London Ambulance Service personnel need to be considered.

The results from the current study provide important comparative data on intravenous lorazepam or rectal diazepam as first line treatment and intravenous phenytoin or rectal paraldehyde as second line treatment for CSE in childhood. With the exception of a longer interval between onset of CSE and arrival to A&E, the clinical characteristics of children that are given initial therapy in hospital with intravenous lorazepam or rectal diazepam are similar and therefore, it is reasonable to compare the treatment outcome between both groups. If children are not given prehospital treatment, in A&E, intravenous lorazepam should be preferred to rectal diazepam as first-line rescue therapy. Despite a longer duration before initial treatment, seizure termination is more likely with intravenous lorazepam than rectal diazepam without increased risk of respiratory depression. In NLSTEPSS, a ten minute interval from administration of an AED to seizure termination was used to assess seizure termination in response to treatment because the pharmacokinetics of the AEDs being examined (intravenous lorazepam, rectal diazepam, intravenous phenytoin and rectal paraldehyde) indicate therapeutic levels are attained within 10 minutes of administration (Knudsen 1977; Walker et al. 1979; Franzoni 1983; Graves 1987; Giang et al. 1988; Walton et al. 1990; Brown et al. 1991). It is beyond the scope of this study to determine whether the increased likelihood of seizure termination observed with treatment with intravenous lorazepam is due to its intrinsically better seizure terminating properties or due to a greater likelihood of being treated with an adequate dose. It is possible that administration of an adequate dose of rectal diazepam may improve its efficacy in seizure termination, but methods to improve the likelihood of treatment with an adequate dose will need to be explored.

The median age, male to female ratio, doses of benzodiazepines administered as first line therapy and other patient and seizure characteristics were similar between children treated with rectal paraldehyde or intravenous phenytoin as second line therapy for CSE. When first-line therapy has failed, the APLS recommended second line drug is rectal paraldehyde but intravenous phenytoin is a commonly used second line treatment worldwide (Scott and Neville 1999). To the candidate's knowledge, this is the first study that suggests that one is superior to the other. In NLSTEPSS, treatment with intravenous phenytoin was associated with a greater likelihood of seizure termination compared to treatment with rectal paraldehyde. The sample size for this comparison of second line agents was small (N=33), but the data do suggest that paraldehyde should not be given as rescue therapy in children with intravenous access.

Randomised controlled trials are expensive, difficult to conduct and particularly in children, fraught with difficulties surrounding consent. Together, these factors make randomised controlled trials on the treatment of CSE in children rare. As outlined in Chapter 2, although randomised controlled trials are considered as the highest level of evidence, there is growing recognition that data from observational studies are useful evidence and in the absence of randomised controlled trials, observational studies may be the highest level of evidence on the optimum treatment of CSE (Cook et al., 1995; Appleton et al., 2000; Scottish Intercollegiate Guidelines Network 2005). Therefore, the data from NLSTEPSS provide important clinical data on the optimum treatment of CSE in childhood and should be utilised in the revision of emergency management strategies for CSE.

The frequency, aetiology, seizure characteristics, treatment and short term outcome of convulsive status epilepticus in a general childhood population were described in this and the preceding chapter. Children referred to a tertiary centre may represent those with the severe end of the spectrum of convulsive status epilepticus, with those requiring admission to a paediatric intensive care unit (PICU) being the most severely affected. Thus, further evaluation of children admitted to PICU for convulsive status epilepticus may provide some insight into determinants of severity.

PART THREE

PICU AND CSE IN CHILDHOOD

CHAPTER 7: PICU AND CONVULSIVE STATUS EPILEPTICUS

7.1 Introduction

Status epilepticus (SE) is the most common neurological emergency in childhood (Leppik 1985; DeLorenzo et al., 1996). Children requiring admission to a paediatric intensive care unit (PICU) for CSE may represent children with the most severe forms of CSE. Thus, identification of factors associated with admission to PICU for CSE may provide some insight into determinants of severity of CSE and the likelihood of refractory CSE, and facilitate the development of appropriate strategies to improve the outcome of CSE. However, studies on admission to PICU for CSE are rare. In the only previously published study on admissions to a paediatric intensive care unit for CSE (Lacroix et al., 1994), 6% of cases died during hospitalisation compared to 3.4% (95% CI 2.7 – 4.1%) in the general childhood population in NLSTEPSS and 78% had neurological deficits at one year follow up. Together these data suggest that there is significant morbidity and mortality associated with CSE requiring admission to PICU. Therapeutic regime may improve the morbidity and mortality associated with CSE by decreasing seizure duration but in the only published study on admission to PICU for CSE, there was sparse information on the pre-PICU treatment of CSE. Therefore, a study that examines the pre-PICU treatment of CSE is required.

The aims of the study reported in this chapter are (1) to characterise the clinical features of children with CSE requiring admission to PICU, (2) to identify factors associated with admission to PICU for CSE, (3) to compare the emergency pre-PICU treatment of CSE to a national guideline for the management of CSE, the APLS guideline and (4) to characterise the course of CSE in children admitted to PICU.

7.2 Methods

7.2.1 Subjects

Subjects eligible for this study were children admitted to a PICU for convulsive status epilepticus. The children were recruited into a larger study of convulsive status epilepticus in childhood described in the previous chapter. They are divided into two groups: (1) prospective and (2) retrospective. As previously stated, children younger than 29 days of age or who had already attained their 16th birthday were excluded.

7.2.2 Data Collection

7.2.2.1 Prospective Group

The prospective part of the study included all children from NLSTEPSS who were admitted to any of the five paediatric intensive care units involved in the population based study in the period May 1, 2002 to April 31, 2004. The methods for case identification and data collection from NLSTEPSS were described in Chapter 5.

7.2.2.2 Retrospective Group

The retrospective aspect of the study consisted of children who were admitted to a paediatric intensive care unit in North London at Great Ormond Street Hospital for Children NHS Trust (GOSH) between April 1, 1998 and March 31, 2001. GOSH is a tertiary paediatric institution in the UK and it's PICU is the main PICU in North London. The study was approved by the GOSH and Institute of Child Health Research Ethics Committee. The diagnoses and demographics for all patients admitted to GOSH's PICU are documented in an admission database. Survival outcome of all admissions is also included. The admission database and discharge

summaries of admissions during the period April 1, 1998 to March 31, 2001 were searched. All potential cases of CSE were identified using the terms: status, epilep*, fit*, seizure* and convuls*, where * indicates that any combination of letters may end the word. The case notes of these potential cases of CSE were systematically reviewed. Episodes of non-convulsive status epilepticus (NCSE) were excluded. Cases with insufficient history or documentation to meet the definition of CSE were excluded. Clinical and demographic data were extracted and recorded using a standard data collection form designed by the candidate (see Appendix 11). As data from this group were obtained from a single institution, results are presented separately for the prospective and overall group.

7.2.3 Definitions

7.2.3.1 Convulsive Status Epilepticus

The definition of convulsive status epilepticus was that described in Chapter 5 i.e. "a seizure with focal or generalised motor manifestations, or series of such seizures between which consciousness is not regained, which last for at least 30 minutes".

7.2.3.2 Seizure type and aetiologies

Seizure type and aetiology were classified independently by the candidate and one of the candidate's supervisors. Disagreements on classifications were resolved by consensus or by third party adjudication. CSE seizure types were categorised as generalised from onset, focal with secondary generalisation, or focal (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). CSE aetiologies were classified using the scheme proposed by the candidate in Chapter 2 i.e. "prolonged febrile seizures, acute symptomatic, acute on remote

symptomatic, remote symptomatic, idiopathic epilepsy related, cryptogenic epilepsy related or unclassified.

7.2.3.3 First and second line AEDs

The pre-PICU emergency management was compared to the APLS guidelines current during the study period i.e. the third edition for the prospective group and the second and third editions for the retrospective group (The Advanced Life Support Group 1997; The Advanced Life Support Group 2000). The second and third editions of the APLS guidelines recommend either lorazepam (administered intravenously) or diazepam (administered intravenously/rectally) as the first line drug and paraldehyde (administered rectally) as the second line drug (see Figure 7.1 for further details on the APLS guidelines).

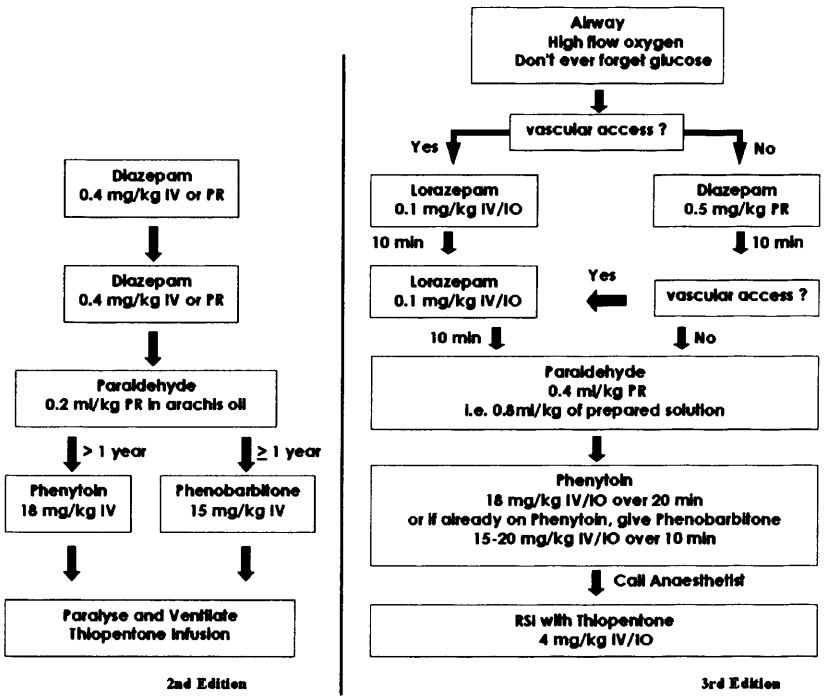

Figure 7.1: APLS algorithms for treatment of convulsive status epilepticus (The Advanced Life Support Group 1997; The Advanced Life Support Group 2000).

7.2.3.4 Adequate doses of first and second line AEDs
7.2.3.4.1 Prospective Group

The adequate dose for intravenous lorazepam is defined as 0.1mg/kg, for rectal diazepam it is 0.5mg/kg, for rectal paraldehyde it is 0.4ml/kg, for intravenous phenytoin it is 18mg/kg and for intravenous phenobarbitone it is 15-20mg/kg (see Figure 7.1). The weight used for calculating adequate doses was that estimated by emergency medical personnel. To allow for any errors in estimating the adequate dose of emergency AED, any administered dose outside 80%-120% of these doses, were considered to be inadequate (low) or high.

7.2.3.4.2 Retrospective Group

The adequate dose of first line and second line drugs was defined as a mean of the recommended doses in the second and third editions of the APLS (see Figure 7.1). Thus, the adequate dose for lorazepam was 0.1mg/kg and for diazepam 0.45mg/kg. The weight used for calculating adequate doses was that documented as the estimated weight used by emergency medical personnel or the measured weight of the child. Where there were differences between weights, the estimated weight was used to determine adequacy of the dose of AED. Allowing for difference in the recommended doses between both APLS guidelines, if the administered dose was outside 80%-120% of the defined adequate doses, it was considered to be inadequate (low) or high. The adequate dose of rectal paraldehyde was determined as above and was 0.3ml/kg. Using the same rationale as above, if the administered dose was less than 50% or greater than 150% of the defined adequate dose, it was considered to be low or high.

7.2.3.5 Reasons for admission to PICU

Primary reasons for admission to PICU were classified into one of the following categories: continuing overt clinical seizure activity, respiratory depression following cessation of clinical seizure activity and decreased consciousness level (Glasgow Coma Scale less than 8).

7.2.4 Statistics

Statistical analyses were conducted in SPSS version 10 (Chicago, Illinois). Kruskal-Wallis ANOVA was used to investigate differences in age according to aetiology of CSE and difference in duration of ventilation according to aetiology of CSE. Chi-Square testing was carried out to examine the relationships between number of doses of benzodiazepine and respiratory depression after seizure termination.

In order to minimise bias, only data from the prospective group were used to identify possible predictors for the need for admission to PICU for CSE. Possible predictors were investigated through forward stepwise multivariate logistic regression analysis. The critical level for entering and removing variables was set at $p=0.05$ and $p=0.1$ respectively. The following variables were investigated: age, ethnicity, sex, incident vs non-incident episode, neurological state prior to episode of CSE, febrile or not, onset in hospital versus onset out of hospital, intermittent vs continuous CSE, focal features or not, interval between onset of CSE and arrival to A&E, treatment with emergency AED within 10 minutes of onset of CSE, treatment with emergency AED within 15 minutes of onset of CSE, adequacy of dose of first AED, treatment with more than 2 doses of benzodiazepines and respiratory depression or not. Repeat episodes of CSE were excluded from this analysis.

7.3 Results

7.3.1 Population and Seizure characteristics

The study population consisted of 184 children with 213 episodes of CSE. Amongst these children, 93 were prospectively identified and had 115 episodes of CSE. The 91 children with 98 episodes of CSE from the retrospective group accounted for 4% of all admission to Great Ormond Street Hospital for Children NHS Trust's PICU over the three year study period. The median age of the children was 2.1 yrs (range 0.1-15.9) and the male to female ratio was 1:1. In the prospective group, the median age of the children was 2.0 yrs (range 0.1-15.9) and the male to female ratio was 1:1. There is no difference in the median age of children when compared according to aetiology (Kruskal-Wallis ANOVA, p = 0.27, see Figure 7.2). Most children were under five years of age (83%) and 75% had incident episodes of CSE.

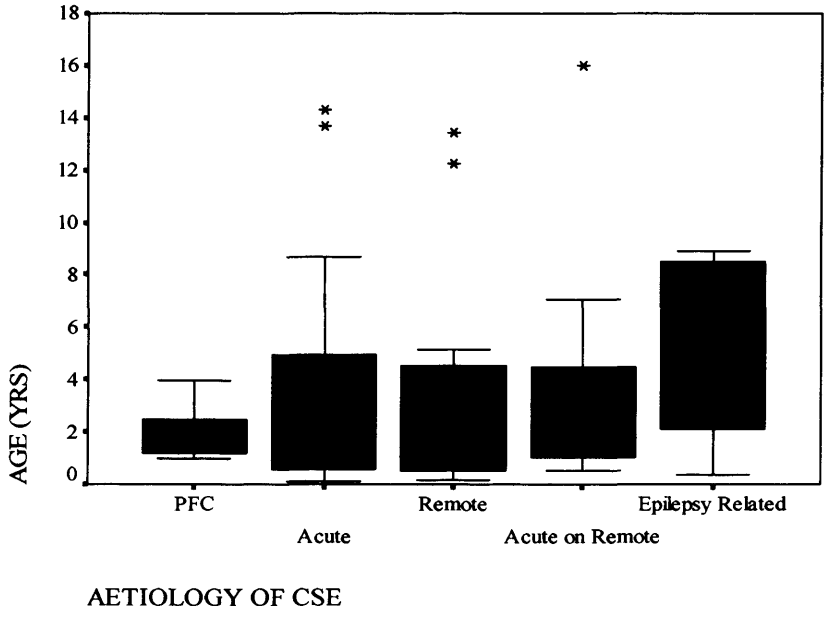

Figure 7.2: Box and Whisker Plot of aetiology of CSE according to age.

The box indicates upper and lower quartiles, the central line within the box is the median and the points at the end of the "whiskers" represent the 2.5% and 97.5% values of the range. An asterisk represents an outlier. There is no difference in the median age between aetiologies (Kruskal-Wallis ANOVA, p=0.30).

7.3.2 Primary reasons for intubation and ventilation

In 51% of children, intubation and ventilation were necessary in order to give medication required to terminate CSE, in 47%, intubation and ventilation were necessary for respiratory insufficiency following successful termination of clinically recognised seizure activity and in 3%, intubation and ventilation were necessary because the children had reduced consciousness (Glasgow Coma Scale score less than 8).

7.3.3 Aetiology of CSE

Similar proportions of CSE occurred in children who had been previously neurologically normal compared to those with pre-existing neurological abnormalities. Approximately one quarter of children admitted to PICU for CSE have prolonged febrile seizures and another quarter have acute symptomatic CSE. Amongst those children admitted to PICU for acute symptomatic CSE, most have a CNS infection or an acute metabolic disturbance (see Table 7.1 for further details on aetiology of acute symptomatic CSE).

7.3.4 Onset of CSE and Final seizure type

Onset of CSE was focal in 38% of children but only 8% of episodes remained focal. In the prospective group, the onset of CSE was focal in 38% of children and 9% of episodes remained focal.

7.3.5 Duration of CSE

The mean duration of CSE was 90 (range 30–435) minutes. The mean duration of CSE in the prospective group was 109 (range 30-660) minutes.

Aetiology of Acute Symptomatic CSE	**All**		**Prospective only**	
	N	%	N	%
CNS infection	32	68	14	58
Acute Metabolic Disturbance	6	13	4	17
Following Hypoxic Episode	2	4	0	0
Subdural Haemorrhage	1	2	0	0
Drug related	1	2	1	4
Head Injury	3	6	3	13
Cerebrovascular Accident	1	2	1	4
Fever	1	2	1	4
All	47	99	24	100

Table 7.1: Aetiology of Acute Symptomatic CSE

The clinical characteristics of the study population are summarised in Table 7.2. The data for the prospective group are presented separately but are substantially similar.

		All	Prospective
PATIENT CHARACTERISTICS			
Age			
	Median (yrs)	2.1	2.0
	Range (yrs)	0.1-15.9	0.1-15.9
	<5 yrs (%)	83	80
M:F		1:1	1:1
CHARACTERISTICS OF CSE			
Incident CSE (%)		77	74
Reasons for Intubation and Ventilation (%)			
	Control of Seizures	51	49
	Respiratory Depression	47	44
	GCS <8	3	6
Aetiology of CSE (%)			
	PFS	28	24
	Acute	22	21
	Remote	14	17
	Acute on Remote	14	20
	Idiopathic Epilepsy Related	15	10
	Cryptogenic Epilepsy Related	3	2
	Unclassified	4	6
Onset			
	Focal	38	38
	Generalised	62	62
Final Seizure Type			
	Focal	8	9
	Generalised	92	91
Duration			
	Mean (mins)	90	109
	Range (mins)	30–435	30-660

Table 7.2: Clinical characteristics of children admitted to PICU for CSE

7.3.6 Emergency pre-PICU treatment of Status Epilepticus

108 children (59% of children admitted to PICU for CSE), of whom 60 were prospectively identified, did not receive prehospital emergency AEDs. In this group of children, the median interval between seizure onset and administration of the first AED in A&E was 35 minutes (n=57, range 10-515 mins) and the median interval between arrival in A&E and seizure termination was 48 minutes (n=58, range 5-180 mins). In the group of children who were prospectively identified, the median interval between seizure onset and administration of the first AED in A&E was 35 minutes (n=28, range 15-515 mins) and the median interval between arrival in A&E and seizure termination was 45 minutes (n=31, range 5-180 mins).

When the overall emergency pre-PICU treatment (prehospital and hospital) was assessed, almost all episodes of CSE (99%) were treated with diazepam or lorazepam as first line AED but their dose was frequently lower (48% of episodes) than that recommended. Of 130 children that were treated with second line AED, paraldehyde was administered in half of episodes. In these, the dose was adequate in 59%.

The choice and adequacy of doses of first and second line AEDs in the pre-PICU treatment of CSE is summarized in Table 7.3

Emergency AED Treatment	All		Prospective Group	
	Prehospital N (%)	Overall N (%)	Prehospital N (%)	Overall N (%)
FIRST LINE AED	184 (100)	184 (100)	93 (100)	93 (100)
Treatment Given	76 (41)	184 (100)	33 (35)	93(100)
Diazepam/Lorazepam	75 (99)	178 (97)	32 (97)	88 (95)
Dose low	49 (65)	85 (48)	21 (66)	48 (55)
Dose adequate	23 (31)	89 (50)	10 (30)	39 (44)
Dose high	3 (4)	4 (2)	1 (3)	1 (1)
Dose unknown	0 (0)	0 (0)	0 (0)	0 (0)
Other	1 (1)	6 (3)	1 (3)	5 (5)
NIL Treatment	108 (59)	0 (0)	60 (65)	0 (0)
SECOND LINE AED	130 (100)	130 (100)	46 (100)	46 (100)
Paraldehyde	-	68 (52)	-	25 (54)
Dose low	-	16 (24)	-	7 (28)
Dose adequate	-	40 (59)	-	17 (68)
Dose high	-	12 (18)	-	1 (4)
Dose unknown	-		-	0 (0)
Phenytoin	-	61 (47)	-	21 (45)
Dose low	-	3 (5)	-	2 (9)
Dose adequate	-	55 (91)	-	19 (91)
Dose high	-	2 (3)	-	0 (0)
Dose unknown	-	1 (2)	-	0 (0)
Phenobarbitone		1 (1)		0 (0)
Dose low	-	0 (0)	-	0 (0)
Dose adequate	-	1 (100)	-	0 (0)
Dose high	-	0 (0)	-	0 (0)
Dose unknown	-	0 (0)	-	0 (0)

Table 7.3: Emergency pre-PICU treatment of Status Epilepticus.

Approximately 6 out of 10 ten episodes of CSE will not be treated in the prehospital setting. Benzodiazepines are the most commonly used first line AED but the dose is frequently low. Similar proportions of episodes of CSE given second line treatment will be treated with paraldehyde and phenytoin but those treated with phenytoin are more likely to receive an adequate dose (chi square = 16.3, $p<0.0005$).

7.3.7 Respiratory depression and number of doses of benzodiazepines

Of the 87 children who developed respiratory depression following seizure termination, 54 (62%) were treated with more than two doses of benzodiazepines. Children given emergency pre PICU treatment that included more than 2 doses of benzodiazepines were more likely to develop respiratory depression than those treated with one or two doses ($\chi^2 = 3.97, p= 0.046$). See Table 7.4 for further detail on the relationship between number of doses of benzodiazepines and respiratory depression.

Doses of Benzodiazepine	**Respiratory Insufficiency**		**Total**
	No	**Yes**	
1or 2	51	33	84
> 2	46	54	100
Total	97	87	184

Table 7.4: The relationship between the number of administered doses of benzodiazepine with respiratory depression after seizure termination $\chi^2 = 3.97, p= 0.046$).

7.3.8 Factors associated with admission to PICU

This analysis was confined to the prospective group to exclude any potential bias that could have resulted from the inclusion of the retrospective group. The following factors were independently associated with admission to PICU for CSE on multivariate regression analysis: respiratory depression, CSE duration > 60 mins compared to CSE lasting 30 – 60 minutes, onset of CSE in hospital rather than out of hospital, incident CSE rather than non-incident CSE and children with previously normal neurology compared to those with a previous neurological abnormality. Treatment with more than 2 doses of benzodiazepines was significant on univariate

analysis (p=0.03) but not on multivariate analysis. Children with CSE lasting longer than 60 minutes were 4 times more likely to be admitted to PICU compared to those whose CSE lasted between thirty and sixty minutes (95% CI 2.2-8.5, p<0.0005). Children with CSE that started in hospital were almost three times more likely (95% CI 1.4 – 5.3, p= 0.004) to require admission to PICU than CSE of out of hospital onset and children who had never had a previous episode of CSE were 2.5 times more likely to be admitted to PICU than those who had previous episodes (95% CI 1.3 – 4.9, p=0.009). Children who were previously neurologically normal were twice as likely to be admitted to PICU as those that had an underlying neurological abnormality (95% CI 1.2 – 4.4, p=0.008). For further details on factors associated with admission to PICU for CSE, see Table 7.5

Variables	***p***	**Odds Ratio**	**95% CI for Odds Ratio**	
			Lower	Upper
Respiratory Depression	<0.00005	238	29.5	1925.7
CSE duration >60 mins	<0.00005	4.3	2.2	8.5
In hospital onset	0.004	2.7	1.4	5.3
Incident CSE	0.009	2.5	1.3	4.9
Previously normal neurological status	0.008	2.3	1.2	4.4

Table 7.5: Multivariate logistic regression model for factors associated with admission to PICU for CSE

7.3.9 Outcome

7.3.9.1 PICU course of CSE

Data on the PICU course of CSE was only available for the retrospective group. In this group of children, the median duration of ventilatory support was 15 hours (n=86,

range 2-168 hrs) and was independent of aetiology (Kruskal Wallis ANOVA, p=0.16). Median length of stay on PICU was one day (range 1-13 days).

7.3.9.2 Mortality

Twelve children (7% of children admitted to PICU for CSE) died. All but one child had no prior episodes of CSE. Five children had acute bacterial meningitis, five children (including the child with previous CSE) had non –specific progressive neurodegenerative disease, one had acute hepatic failure and one had a brain tumour.

7.4 Discussion

The purpose of the current study was to characterise a population of children requiring admission to PICU within the context of an episode of CSE to provide a framework for strategies that reduce requirement for admission to PICU. The need for intensive care management of CSE may be related to severity of CSE and there may be particular clinical characteristics of such cases that are distinct from those in cases of CSE in the general population. Admissions to PICU for CSE may also be due to inadequate pre-PICU emergency treatment.

The data from this study suggest that the clinical factors associated with admission to PICU for CSE are the development of respiratory depression, CSE lasting longer than 60 mins, CSE that starts in hospital, incident episodes of CSE and previously normal neurological status. On this evidence strategies to reduce the risk of respiratory depression and to reduce the likelihood of CSE of duration longer than 60 minutes may contribute to a reduction in admissions to PICU for CSE.

In comparison with the Canadian PICU study (Lacroix et al., 1994), a greater

proportion of children with CSE in this series was admitted to PICU for respiratory insufficiency following seizure termination (48% vs 8%). Compared to a prospective study of children presenting to A&E with seizures, this study reports a similar proportion of children requiring ventilation for respiratory depression associated with administration of benzodiazepines (48% vs 57%) (Hui et al., 2003). The data from the current PICU study, suggest that respiratory depression is more likely in children who are treated with more than two doses of benzodiazepines and treatment with more than two doses of benzodiazepines was associated with prehospital treatment. These findings are consistent with those from the population based study reported in Chapter 6 and provide further support for the view that not taking prehospital treatment into account will contribute to the risk of respiratory depression associated with CSE. Therefore, the entry point into the guidelines for the management of CSE needs to be clarified to minimise the risk of treatment with more than two doses of benzodiazepines.

The number of doses of benzodiazepine is not the only concern relating to the emergency pre PICU treatment of CSE. There are also treatment delays and poor adherence to recommended doses. The data from this series suggest that only one in every eight children with CSE admitted to PICU is appropriately treated prior to arrival in A&E. When the overall emergency pre-PICU treatment is assessed, the doses of APLS recommended first and second line drugs are commonly low. In previous studies, including NLSTEPSS, prehospital treatment is one of the factors associated with a shorter duration of CSE (Alldredge et al., 1995; Alldredge et al., 2001) and thus, it is conceivable that widespread prehospital treatment may decrease admissions to PICU for CSE.

Rectal paraldehyde is the APLS recommended second line therapy for CSE but similar proportions of children admitted to PICU for CSE were treated with rectal paraldehyde or intravenous phenytoin as second line therapy prior to arrival to PICU. Intravenous phenytoin , although not in the APLS guideline as a second line drug, is widely considered to be an appropriate second-line agent (Scott and Neville 1999). There is no previously published evidence that either is superior to the other as a second line drug (Logroscino et al., 2002) but data from NLSTEPSS suggest that second line treatment with intravenous phenytoin is more likely to result in seizure termination than treatment with rectal paraldehyde. Therefore admissions to PICU for CSE may be reduced if intravenous phenytoin rather than rectal paraldehyde is preferred second line therapy for the treatment of CSE in childhood.

Should a seizure continue for longer than forty minutes after the initiation of treatment, the APLS guideline suggests induction of anaesthesia with thiopentone and endotracheal intubation and ventilation. In A&E, medical teams managing children with CSE are adhering to this forty minutes time line, as the observed interval between arrival to hospital and seizure termination is similar. Thus, in order to limit seizure duration strategies to improve prehospital management need to be considered.

The use of intravenous agents in the prehospital setting is limited by the difficulty in gaining intravenous access in children, especially in those aged less than 5 years (Lillis and Jaffe 1992). Rectal preparations, as are currently used, are limited by concerns over social unacceptability or inconvenience of administering rectal drugs. Recent studies on benzodiazepines by the buccal (Scott et al., 1998; Scott et al. 1999) or nasal (O'Regan et al., 1996) route have reported similar efficacy to rectal diazepam without increased risk of adverse effects. Thus, there may be alternative

medications that are easier and more socially acceptable to administer. Implementation of such agents may result in improvement in the number of children successfully treated in the prehospital setting and thereby reduce the number of children requiring intensive care treatment for CSE.

7.5 Conclusions

In this chapter, the candidate aimed to characterise a population of children requiring admission to PICU for CSE to provide a framework for strategies that reduce the requirement for admission to PICU and to provide some insights into determinants of severity of CSE. The study population is made of a prospective group obtained through NLSTEPSS and a retrospective group obtained from admissions to the largest and busiest PICU in North London. Therefore, the retrospective group is likely to be a representative sample of children from North London that require intensive care.

The data from the study in this chapter suggest that CSE that starts in hospital, incident episodes of CSE and previously normal neurological status may be important clinical markers for an increased likelihood for admission to PICU. Strategies to reduce the risk of respiratory depression and to reduce the likelihood of CSE of duration longer than 60 minutes may contribute to reduction in admissions to PICU for CSE. Lack of prehospital treatment increases the likelihood of CSE lasting longer than 60 minutes and it may be hypothesised that widespread prehospital treatment may reduce the likelihood of such seizures. Since the administration of more than two doses of a benzodiazepine is associated with an increased risk of respiratory depression, prehospital treatment should be taken into account during further treatment. It is proposed that guidelines for the management of CSE should be revised to take into account the above findings.

PART FOUR

CONCLUSIONS AND FUTURE DIRECTIONS

CHAPTER 8: CONCLUSIONS

The overall aims of this study were, through a population based study on a paediatric population, to characterise the frequency, aetiology and short term outcome of CSE in childhood and to identify possible factors associated with longer duration of CSE and admission to PICU. A population based study was conducted because data from hospital based studies may result in biased information which may not be applicable to the general population. The systematic review of the epidemiology of CSE reported in Chapter 2 illustrates that all previously available population based information on CSE is biased towards an adult population rather than a paediatric population, but data from adults may not be directly applicable to children. Therefore this study was confined to a paediatric population. In order to maximise ascertainment of cases, a multi source identification system was utilised and capture-recapture methodology was used to estimate the degree of ascertainment. Longer duration of CSE is associated with increasing morbidity and mortality of CSE (Aicardi et al., 1970; Meldrum et al. 1973; Yager et al., 1988; Dunn 1988; Logroscino et al., 1997; Logroscino et al., 2002; Hui et al., 2003) and admission to PICU is associated with CSE refractory to treatment (Walker et al., 1995; Walker et al., 1996; Sahin et al., 2001; Sahin and Riviello 2001). Therefore, identification of factors associated with longer duration of CSE and admission to PICU for CSE may provide the basis for the development of strategies to improve the outcome of CSE.

The results of the North London convulsive STatus Epilepticus in childhood Surveillance Study (NLSTEPSS), show that in North London, the ascertainment

adjusted incidence of CSE in childhood is estimated to be 17-23/100,000 children /yr and the ascertainment adjusted occurrence is 30-41/100,000 children /yr. Extrapolating these data to the population of England and Wales, an estimated 1450 to 2250 children per year will have a life time first episode of CSE and there are least 2700 to 4300 episodes of CSE that require attendance to hospital for emergency treatment. Factors that influence the overall incidence of CSE are ascertainment methods, age, sex, ethnicity and socioeconomic status. The results of this study confirm the greater likelihood of underascertainment in single sources of ascertainment compared to multiple sources and demonstrate the effectiveness of using capture-recapture for more than the commonly used two sources. The incidence of CSE is higher in children aged less than 5 years compared to those 5 years and older, with the peak incidence in those aged less than one year. The incidence is also higher in males compared to females and in non-white, but not black, children compared to white children and in children of lower socioeconomic status compared to those of higher socioeconomic status. Previous studies have reported a higher incidence in non-white populations than white populations (DeLorenzo et al., 1996; Coeytaux et al., 2001) but the role of socioeconomic status has not been previously reported. This is the first study which has demonstrated the independent effects of socioeconomic status and ethnicity on the incidence of CSE and hence, results of previous studies that reported ethnic/race differences in the incidence of CSE (DeLorenzo et al., 1996; Coeytaux et al., 2001) may have been confounded by the socioeconomic composition of their study populations. The data from NLSTEPSS also suggest that widespread use of prehospital treatment of seizures may decrease the incidence of CSE. NLSTEPSS, was restricted to children who ultimately had seizures lasting at least thirty minutes. Most seizures lasting less than five minutes will

terminate spontaneously and increasing seizure duration is associated with increasing difficulty in seizure termination (Knudsen 1979; Sykes and Okonofua 1988; Shinnar et al., 2001a). Thus, the group of children in NLSTEPSS had difficult to control seizures. Prehospital treatment in this group of children decreased the likelihood of CSE lasting longer than 60 minutes than 30-60 minutes. Therefore, it is possible that prehospital treatment of all seizures that last at least five minutes will decrease the likelihood of seizures lasting at least thirty minutes.

The above data are consistent with genetic, environmental and prehospital treatment influences on the development of CSE and therefore, even using similar quality study methodologies, studies may obtain different estimates of the incidence of CSE according to the study population. The highest crude incidence of convulsive status epilepticus in children in the published literature has been reported by the Richmond, Virginia group, (27/100,000 children /yr) and has been largely attributed to the prospective nature of the study, high ascertainment and a higher incidence in a black population than a white population; Richmond has a predominantly black population. As only 29 children were recruited into the two year study period, the estimate lacks a high degree of precision; the 95% confidence interval of the incidence is 11-43/100,000 children/yr. Ascertainment in the current prospective study is at least as good as the Richmond study, but the crude incidence is lower than that reported in the Richmond group and there is no difference in the black population compared to the white population. It is possible that the differences in the relationship of ethnicity and incidence of CSE between the two studies are due to differences in the categorisation of ethnicity. In the UK, families are defined as belonging to an ethnic group according to whatever they consider their ethnic group. Nonetheless, taking the data

from this study into account and that Richmond has a poor population, the candidate proposes that the higher incidence reported by the Richmond group is less attributable to degree of ascertainment but significantly attributable to the socioeconomic composition of the population and the higher incidence reported in the black population has been confounded by this factor.

Prolonged febrile seizures account for a third of incident episodes of CSE and are the most common form of CSE in childhood. This distinct form of CSE occurs only in childhood and has been largely ignored in previous population based studies. As discussed in Chapter 1, a classification system, such as that recommended by the ILAE, that includes prolonged febrile seizures in the same category as SE due to an identified acute CNS infection, may be inappropriate for paediatric epidemiological or outcome studies. The morbidity and mortality associated with prolonged febrile seizures is low (Nelson and Ellenberg, 1978; Maytal et al., 1990; Verity et al., 1993; Shinnar et al., 2001b; Wu et al., 2002), which is in sharp contrast to the high morbidity and mortality associated with acute CNS infections (Goldacre 1976; Shaltout et al., 1989; Dagan 1994; Berg et al., 1996; Pongbhaesaj et al., 2004; Tyler 2004). Therefore, the results of studies on status epilepticus in childhood that utilise the current ILAE classification, may erroneously amplify the severity of outcome of prolonged febrile seizures and conversely, dilute the severity of acute neurological insults. In NLSTEPSS, the candidate has illustrated that it is possible to use an alternative classification system for the aetiologies of convulsive status epilepticus, one in which prolonged febrile seizures is considered a distinct category. In NLSTEPSS, there were no deaths associated with prolonged febrile seizures whilst three children with acute bacterial meningitis died i.e. the case fatality of prolonged

febrile seizures was 0% and the case fatality of acute symptomatic CSE was 9%. Had prolonged febrile seizures not been considered a distinct category, case fatality associated with acute symptomatic CSE would have been three times lower. Investigating the morbidity associated with CSE was not an aim of this study, but is an important question that may be addressed in future studies.

The precise pathophysiological mechanisms for prolonged febrile seizures are unknown but there is evidence of a genetic predisposition. By using the alternative classification system used in NLSTEPSS, the candidate was able to identify a distinct group of patients with prolonged febrile seizures. In a subgroup analysis, Asian children had the highest incidence of prolonged febrile seizures. Thus, to understand the genetic mechanisms surrounding prolonged febrile seizures, it is possible that initial investigations may be best directed at an Asian population.

Children with pre-existing neurological abnormalities may have a lower seizure threshold compared to those who are neurologically normal and in the course of an intercurrent illness, it may be impossible to distinguish whether CSE is due to the underlying abnormality, the intercurrent illness, or both. Therefore, in an attempt to distinguish such children from neurologically normal children with prolonged febrile seizures, the candidate included the designation "acute on remote symptomatic" amongst the aetiologies of CSE. Through the classification used in NLSTEPSS, the candidate has successfully been able to identify three distinct groups of children with CSE associated with fever. Follow up studies on these distinct groups will provide a much clearer picture on their outcome. The three main features of febrile seizures associated with the subsequent development of epilepsy are prolonged duration,

recurrent seizures and focal features (Seki et al., 1981; Annegers et al., 1987; Maher and McLachlan 1995; Shinnar et al., 2001b; Trinka et al., 2002). Up to twenty percent of children with any two features and up to fifty percent of children with all three features will develop epilepsy (Annegers et al., 1987). Since a quarter of children with prolonged febrile seizures in this study had focal features, it is anticipated that a significant number will develop epilepsy. The data from this study also demonstrate that there is a significant risk of acute CNS infection in children with lifetime first episodes of CSE and therefore there should be a low threshold for empirical treatment with parenteral antibiotics and antiviral agents.

In NLSTEPSS, aetiologies of CSE were classified according to strict definitions and classification was reliant on clinical features of patients on presentation and the results of all investigations. This study was observational and as the degree of investigation varied, the candidate recognises that it is entirely possible that some of the children may have been classified into a different category if their investigations were different. To minimise this likelihood, all outstanding results of investigations requested by the consultant(s) managing the child were collated within six to eight weeks after initial presentation to hospital.

This study provides epidemiological evidence which strongly supports the role of prehospital treatment in the emergency management of CSE in childhood. CSE frequently has an onset out of hospital and there are animal and human studies supporting the hypothesis that delayed treatment of seizures is associated with increasing difficulty in seizure termination. In addition, delayed treatment is associated with increased risk of death (Hui et al., 2003). In this study, lack of

prehospital treatment was independently associated with CSE lasting longer than 60 minutes compared to CSE lasting between 30 to 60 minutes. Therefore, widespread prehospital treatment of CSE may improve the outcome of CSE but prehospital treatment is not yet universal practice. In many parts of the USA and Canada, patients have traditionally been transported to hospital as soon as possible for initiation of treatment in the emergency room (Emergency Paediatrics Section 1996; Alldredge et al., 2001; Lowenstein et al., 2001). A recent seminal study by Alldredge and colleagues has demonstrated the benefit and safety of prehospital treatment with intravenous therapy in adults (Alldredge et al., 2001) but in children the use of intravenous agents is limited by the difficulty in gaining intravenous access, especially in those aged less than 5 years, the age group most likely to have CSE. Only recently in the USA has there been a widespread emerging use of rectal diazepam in the prehospital treatment of CSE.

Rectal preparations, as are currently used, are limited by concerns over social unacceptability or inconvenience of administering a rectal drug. Recent studies on benzodiazepines by the buccal or nasal route have reported similar efficacy and even superior efficacy to rectal diazepam without increased risk of adverse effects (O'Regan et al. 1996; Scott et al., 1998; Scott et al. 1999; Camfield 1999; Whitehouse et al., 2005). Thus, there may be alternative medications that are easier and more socially acceptable to administer.

It is not only important to begin treatment in the prehospital setting, the initial dose also needs to be adequate. Prepackaged preparations of non intravenous emergency AEDs, as are currently available, make it difficult to titrate adequate doses of the

emergency AEDs. Alternative graduated preparations of emergency AEDs may increase the likelihood of administration of adequate doses of AEDs. Failing that, carers and or emergency personnel may need to consider practical ways to deliver a titred, adequate dose of a suitable emergency AED. One such possibility is to measure the dose of AED with a syringe before administration. Thus, prehospital treatment with an adequate first dose of a suitable emergency AED may improve the outcome of CSE but who should administer such treatment? The data from NLSTEPSS suggest that parents are willing to treat children in the prehospital setting if emergency treatment is available to them. More than half of children who had a previous episode of CSE were treated initially by their parents at home in subsequent episodes of CSE and in children with a previous neurological abnormality and an incident episode of CSE (n=78), 17% were treated initially by their parents at home. None of the children in this North London cohort developed obvious respiratory depression following initial treatment of CSE at home, however most received an inadequate dose. In children with pre-existing neurological abnormalities, previous studies have demonstrated the effectiveness of home treatment with emergency AEDs in the early termination of seizures, but there is a risk of respiratory depression (Hoppu and Santavuori 1981; Camfield et al., 1989; Kriel et al., 1991). On the basis of these findings, it would seem reasonable to make emergency AEDs more widely available for parents with children with pre-existing neurological abnormalities. However, as there is a risk of respiratory depression and use of AEDs for potentially harmful non-medical reasons, paediatricians will need to be selective in determining which parents are allowed to administer emergency AEDs. Half of children with CSE are previously neurologically normal, and therefore initial treatment of such children may only be administered by emergency medical personnel. However, in this study,

approximately half of incident cases transported to hospital by ambulance were not given any prehospital treatment, despite the existence of a stated treatment guideline by the London Ambulance Service for children with CSE. Thus, strategies to improve prehospital treatment by ambulance personnel need to be explored.

The data from this study confirms the previously reported increased likelihood of respiratory depression associated with treatment with more than two doses of benzodiazepines (Dieckmann 1994; Norris et al., 1999; Rainbow et al., 2002; Stewart et al., 2002). In addition, the data suggest that children that fail to respond to 2 doses of benzodiazepine have CSE refractory to benzodiazepines and should not receive further doses. Therefore, it is proposed that the use of benzodiazepines in the emergency treatment of CSE in childhood should be limited to two doses. In their current state, the UK national treatment guidelines for the emergency treatment of CSE in childhood are ambiguous as to whether prehospital treatment should be taken into account or state that it should be disregarded (Advanced Life Support Group 2002; The Advanced Life Support Group 2005). The data from this study would suggest that clinicians in A&E should regard prehospital treatment as part of the emergency treatment of CSE in childhood and therefore, if two doses of benzodiazepines have been given prior to arrival at hospital, the initial treatment in hospital should be second line therapy.

Randomised controlled trials are expensive, difficult to conduct and in children, are fraught with difficulties with consent. These factors make RCTs in children rare and the likelihood of RCTs investigating intravenous lorazepam or rectal diazepam as first line emergency AED and intravenous phenytoin or rectal paraldehyde as second line

emergency AED for the treatment of CSE in childhood, is small. In the absence of RCTs, observational studies may be the highest level of evidence for the optimum treatment of CSE in childhood. The data from the current observational study suggest that in A&E, intravenous lorazepam may be better first line therapy than rectal diazepam and children with intravenous access should not be treated with rectal paraldehyde as second line rescue therapy.

If the treatment data from Chapters 6 and 7 are considered together, they indicate that guidelines for the management of CSE may need to be revised to take into account their findings and a new guideline proposed by the candidate is illustrated in Figure 8.1.

In summary, the results of this study support the view that CSE in childhood is common and that prolonged febrile seizures are the most common type of CSE in childhood. In order to further understand the pathophysiological mechanisms of prolonged febrile seizures, including the genetic mechanisms, an attempt to categorise such forms of CSE in a distinct group should be considered. Genetic, environmental and treatment factors may influence the incidence and outcome of CSE. Prehospital treatment may improve the outcome of CSE by decreasing the duration of CSE and there are data that suggest that first and second line emergency treatment of CSE by the intravenous route is superior to treatment by the rectal route. This study also provides information on the significant risk of admission to PICU (half of incident cases and a third of all occurrences of CSE), the significant risk of recurrence within a year (one in six children with an incident episode of CSE) and the short term mortality associated with CSE (case fatality of 3%). However, the neurocognitive outcome, the

risk of subsequent development of epilepsy, the risk of mesial temporal sclerosis and the long term mortality associated with CSE in childhood remain unclear and further research addressing these areas is needed.

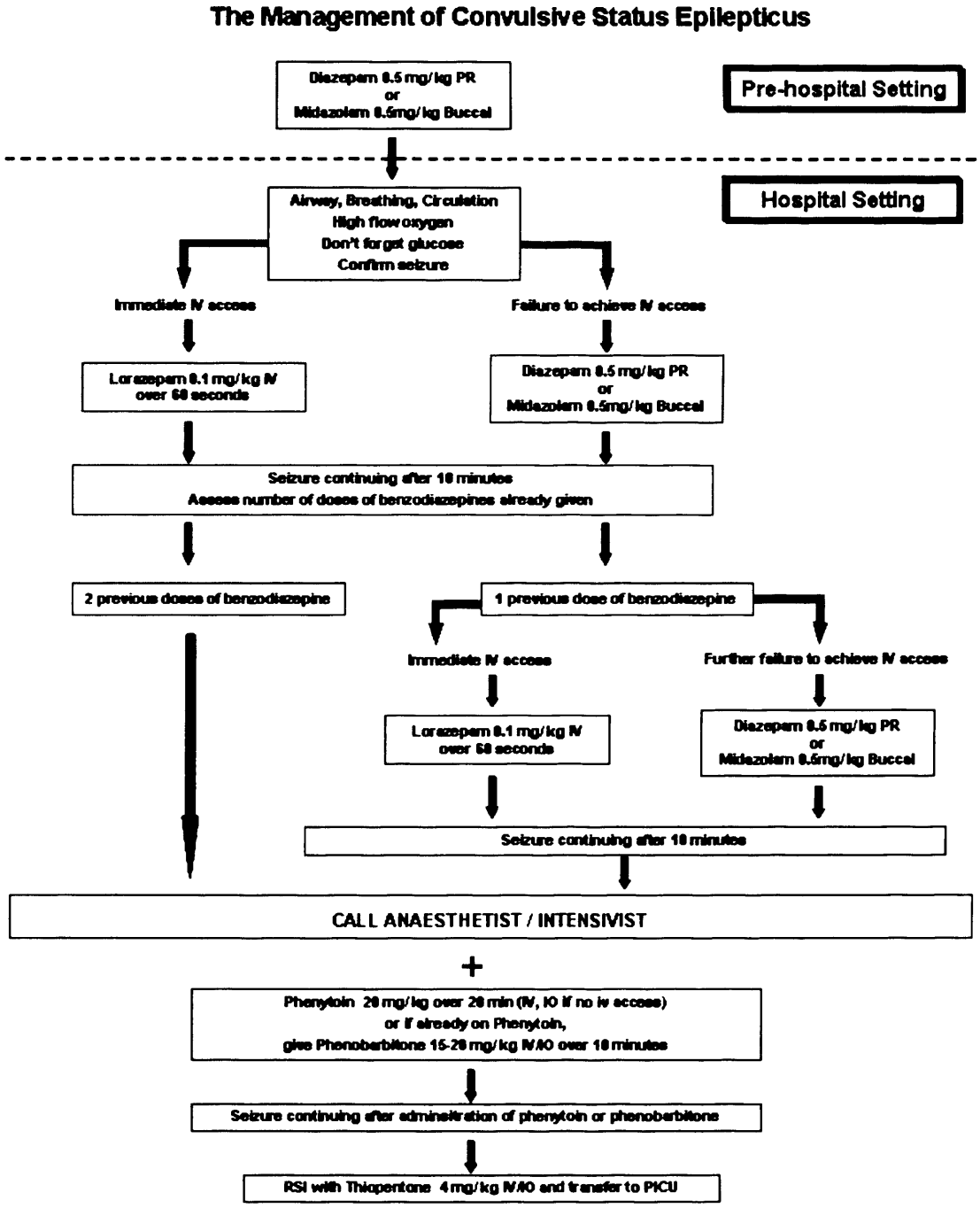

Figure 8.1: Proposed treatment guideline for convulsive status epilepticus in childhood.

CHAPTER 9: FUTURE DIRECTIONS

To investigate the neurocognitive outcome, the risk of subsequent development of epilepsy, the risk of mesial temporal sclerosis and long term mortality associated with CSE in childhood, longitudinal studies on a cohort of children with CSE are required. The cohort of patients identified in NLSTEPSS would be suitable for such studies but more patients would be required to increase the sample size. This could be achieved by an extension of the ascertainment methodology already used in NLSTEPSS. Longitudinal studies on the morbidity associated with CSE may include MRI investigations and comprehensive neurological and neurocognitive assessments of children with CSE.

There is already ongoing magnetic resonance (MR) research based in North London examining the hypothesis that there is a causative relationship between prolonged febrile seizures and mesial temporal sclerosis (Scott et al., 2002; Scott et al., 2003) but the possible association of other forms of CSE and MTS has not been investigated. To date, the research has been centred on a small number (14) of patients who were investigated with MRI within 5 days of a prolonged febrile seizures and 4-8 months thereafter. MR studies on a large cohort of children with CSE could provide longitudinal MR data at discrete short, medium and long term time intervals on a much greater number of children with all forms of CSE. A time line on the pathological changes that occur in the different forms of CSE could be established and would provide the basis for the development of potential anti-epileptic and or neuroprotective strategies. MR investigations could be coordinated to allow for neurological and neurocognitive assessments on the same day.

Prehospital treatment is associated with a shorter duration of seizure activity in this population of children who all had seizures ultimately lasting at least 30 minutes and therefore had difficult to control seizures. This leads to the hypothesis that widespread prehospital treatment of seizures that do not spontaneously terminate within five minutes may decrease overall duration of seizure activity and decrease the potential morbidity and mortality associated with prolonged seizure activity. Audits of prehospital treatment of children transported to A&E by ambulance for seizures would provide important data addressing this hypothesis. In addition, audits of prehospital treatment of children with seizures may identify factors for non-treatment or inadequate treatment of seizures in the prehospital setting. Such data may serve as the basis for development of strategies to improve prehospital treatment of seizures.

The data from the current study provides evidence in support of the role of prehospital treatment in the management of seizures. Within the published literature there is only one randomized controlled trial comparing possible prehospital emergency treatment of seizures in children (Scott et al. 1999). In that study, which was conducted in a population of children with severe epilepsy, enrolled in a residential school, buccal midazolam was found to be at least as effective as rectal diazepam. However, it is unclear whether it would be effective in the community, in younger children and children who were previously healthy. To explore the most effective treatment of seizures in the prehospital setting, large community based randomised controlled trials will need to be conducted.

There is accumulating evidence for the likelihood of brain damage following prolonged febrile seizures having a genetic component. A family history of febrile

seizures is a major risk factor for febrile seizures in offspring (Waruiru and Appleton 2004); there is a 38% risk of SE amongst co-twins of monozygotic twins who experienced SE (Corey et al., 1998; Corey et al. 2004); polymorphisms in the interleukin-1gene, a gene that encodes a proinflammatory cytokine that modulates neurotoxic neurotransmitters, are associated with TLE and hippocampal sclerosis (Kanemoto et al., 2000; Kanemoto et al., 2003). Despite these data regarding possible genetic factors in the occurrence of prolonged febrile seizures and of seizure-induced injury, little is known about the precise genes involved or the mechanism by which their influence might be exerted (Cendes et al., 1998; Heils et al., 2000; Kobayashi et al., 2001; Baulac et al., 2001; Depondt et al., 2002; Jin et al., 2003; Kobayashi et al., 2003). Identification of family pedigrees with a history of prolonged febrile seizures from the NLSTEPSS cohort would facilitate linkage studies. Multi-centre international collaboration amongst research groups with cohorts of children with CSE would improve the likelihood of detection of gene polymorphisms associated with prolonged febrile seizures and seizure induced brain injury.

In the present work, lower socioeconomic status was independently associated with an increased incidence of CSE, suggesting potential environmental influences on the development of status epilepticus. However, the precise socioeconomic factors that predispose to an increased risk of CSE remain uncertain. Younger maternal age (<25 years), high school education or less, low income, maternal smoking and alcohol consumption during pregnancy, single marital status, little contact with neighbours and depression are associated with an increased risk of perinatal problems (Peacock et al., 1995; Phares et al., 2004). Maternal smoking and alcohol consumption during pregnancy are also associated with the development of febrile seizures during

childhood (Cassano et al., 1990; Nelson and Ellenberg 1990). A study involving detailed structured interviews of families of a cohort of children with CSE may provide some insight into possible environmental factors associated with an increased risk of CSE.

The North London convulsive STatus EPilepticus in childhood Surveillance Study is a major epidemiological study. The results will advance the understanding of convulsive status epilepticus and may provide the foundations for improvement in the management of convulsive status epilepticus. Data obtained may serve as the basis for the development of preventative and improved treatment strategies and have lead to the generation of hypotheses surrounding the causal pathways and mechanisms underlying convulsive status epilepticus in childhood. The prospects for research addressing these areas as well as the morbidity associated with CSE are very exciting with the potential of making significant improvements to the lives of children.

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CHAPTER 11: APPENDICES

Appendix 1: Glossary of definitions for the systematic review of population based studies of status epilepticus described in Chapter 2.

DEFINITIONS

1. Status Epilepticus

All studies considered SE as a single seizure or series of seizures without recovery of consciousness between seizures lasting at least thirty minutes. The Californian study by Wu and colleagues (Wu et al., 2002) excluded non-convulsive SE.

2. Incident cases

The Rochester study (Hesdorffer et al., 1998) defined incident cases as lifetime first cases of SE. The Californian study (Wu et al., 2002) defined incident cases as cases that were admitted to hospital for the first time with SE in the seven-year study period. Incident cases were not clearly defined in the other studies.

3. Age groups

The age groups in the individual study groups are listed in Table A.1.

4. Aetiology

The Californian group's study listed aetiologies (Wu et al., 2002) while five studies (DeLorenzo et al., 1996; Hesdorffer et al., 1998; Knake et al., 2001; Coeytaux et al., 2001; Trevathan et al. 2002) used a classification system for aetiologies which was similar across research groups. Aetiologies were classified as either provoked (acute

symptomatic) or unprovoked. Unprovoked aetiologies were either remote symptomatic or idiopathic/cryptogenic (unknown aetiology) (DeLorenzo et al., 1996; Hesdorffer et al., 1998; Coeytaux et al., 2001; Knake et al., 2001). In two studies, remote symptomatic aetiologies were further classified into those with static CNS lesions and those with progressive CNS lesions (Hesdorffer et al., 1998; Coeytaux et al., 2001). In two studies, SE was associated with multiple aetiologies (DeLorenzo et al., 1996; Knake et al., 2001). prolonged febrile seizures, defined as SE occurring in a febrile illness among children in the absence of another acute symptomatic cause, including CNS infection, was classified as a special class of acute symptomatic SE in the Rochester and North London groups (Hesdorffer et al., 1998; Treiman et al., 1998).

5. Association with epilepsy

Epilepsy was defined in two of the studies and was defined as two or more seizure episodes in a lifetime (DeLorenzo et al., 1996; Coeytaux et al., 2001).

6. SE Seizure Types

The classification of SE type was similar in all studies except the Waterhouse study from the Richmond Group that classified SE into continuous or intermittent. All studies divided seizure types initially into partial seizures and generalised seizures. Except for the Waterhouse study, all studies further divided the partial seizure group into simple partial, complex partial, and partial with secondary generalisation and generalised seizures were divided into tonic, clonic, tonic-clonic, myoclonic, and

absence/non-convulsive status epilepticus. Two studies had a separate categorisation for seizures that were diagnosed on EEG findings only (subtle SE) (DeLorenzo et al., 1996; Coeytaux et al., 2001), one had a category for unknown seizure type (Knake et al., 2001), and one had a hemi-convulsive seizure category (Coeytaux et al., 2001).

7. Recurrence of SE

The Richmond Group defined recurrence as another episode of SE occurring within a two-year follow-up period following an initial episode of SE. The Knake study defined recurrence as further episodes of SE during the 2 year study period. The Rochester Group did not define recurrence but their retrospective study examined a twenty year period.

8. Short term mortality

Three studies defined mortality as the proportion of deaths within 30 days of the cases of incident episode of SE (DeLorenzo et al., 1996; Hesdorffer et al., 1998; Knake et al., 2001), one study defined it as the proportion of deaths within 60 days of the incident episode (Waterhouse et al. 1999), and three studies defined it as the proportion of hospital deaths (Coeytaux et al., 2001; Trevathan et al., 2002; Wu et al., 2002).

9. Long term mortality

The Rochester group defined long term mortality as the number of deaths after initial survival for 30 days after intial episode of SE within the population, within 10 years.

Age Groups	Richmond	Rochester	Germany	Switzerland	California	St. Louis
Children	31 days - 15 yrs	Birth - 14 yrs	Excluded	Birth - 14yrs	Birth - 19 yrs	31days - 16yrs
Adults	16 - 59 yrs	15-64 yrs	18 - 59 yrs	15-59 yrs	20-54 yrs	17-65 yrs
Elderly	60 yrs and over	65 yrs and over	60 yrs and over	60 yrs and over	55 yrs and over	65 yrs and over

Table A.1: Age groups according to research group.

Appendix 2: Dimensions of Deprivation for IMD 2004 (Office of National Statistics 2004)

Dimensions of Deprivation for IMD 2004	Weighting	Indicators
Income deprivation	22.5%	Adults and children in Income Support households (2001).
		Adults and children in Income Based Job Seekers Allowance households (2001).
		Adults and children in Working Families Tax Credit households whose equivalised income (excluding housing benefits) is below 60% of median before housing costs (2001).
		Adults and children in Disabled Person's Tax Credit households whose equivalised income (excluding housing benefits) is below 60% of median before housing costs (2001).
		National Asylum Support Service supported asylum seekers in England in receipt of subsistence only and accommodation support (2002).
Employment deprivation	22.5%	Unemployment claimant count (JUVOS) of women aged 18-59 and men aged 18-64 averaged over 4 quarters (2001).
		Incapacity Benefit claimants women aged 18-59 and men aged 18-64 (2001).
		Severe Disablement Allowance claimants women aged 18-59 and men aged 18-64 (2001).
		Participants in New Deal for the 18-24s who are not included in the claimant count (2001).
		Participants in New Deal for 25+ who are not included in the claimant count (2001).
		Participants in New Deal for Lone Parents aged 18 and over (2001).
Health deprivation and Disability	13.5%	Years of Potential Life Lost (1997-2001).
		Comparative Illness and Disability Ratio (2001).
		Measures of emergency admissions to hospital (1999-002).
		Adults under 60 suffering from mood or anxiety disorders (1997-2002).
Education, skill and training deprivation	13.5%	Average points score of children at Key Stage 2 (2002).
		Average points score of children at Key Stage 3 (2002).
		Average points score of children at Key Stage 4 (2002).
		Proportion of young people *not* staying on in school or school level education above 16 (2001).
		Proportion of those aged under 21 not entering Higher Education (1999-2002).
		Secondary school absence rate (2001-2002).
		Proportions of working age adults (aged 25-54) in the area with no or low qualifications (2001

Housing and Services	9.3%	Household overcrowding (2001)
		LA level percentage of households for whom a decision on their application for assistance under the homeless provisions of housing legislation has been made, assigned to SOAs (2002).
		Difficulty of Access to owner-occupation (2002).
		Road distance to GP premises (2003).
		Road distance to a primary school (2001-2002).
		Road distance to a Post Office (2003)
		Road distance to a supermarket or convenience store (2002).
Crime	9.3%	Burglary (4 recorded crime offence types, April 2002-March 2003).
		Theft (5 recorded crime offence types, April 2002-March 2003, constrained to CDRP level).
		Criminal damage (10 recorded crime offence types, April 2002-March 2003).
		Violence (14 recorded crime offence types, April 2002-March 2003).
Living Environment deprivation	9.3%	Social and private housing in poor condition (2001).
		Houses without central heating (2001).
		Road traffic accidents involving injury to pedestrians and cyclists (2000-2002).

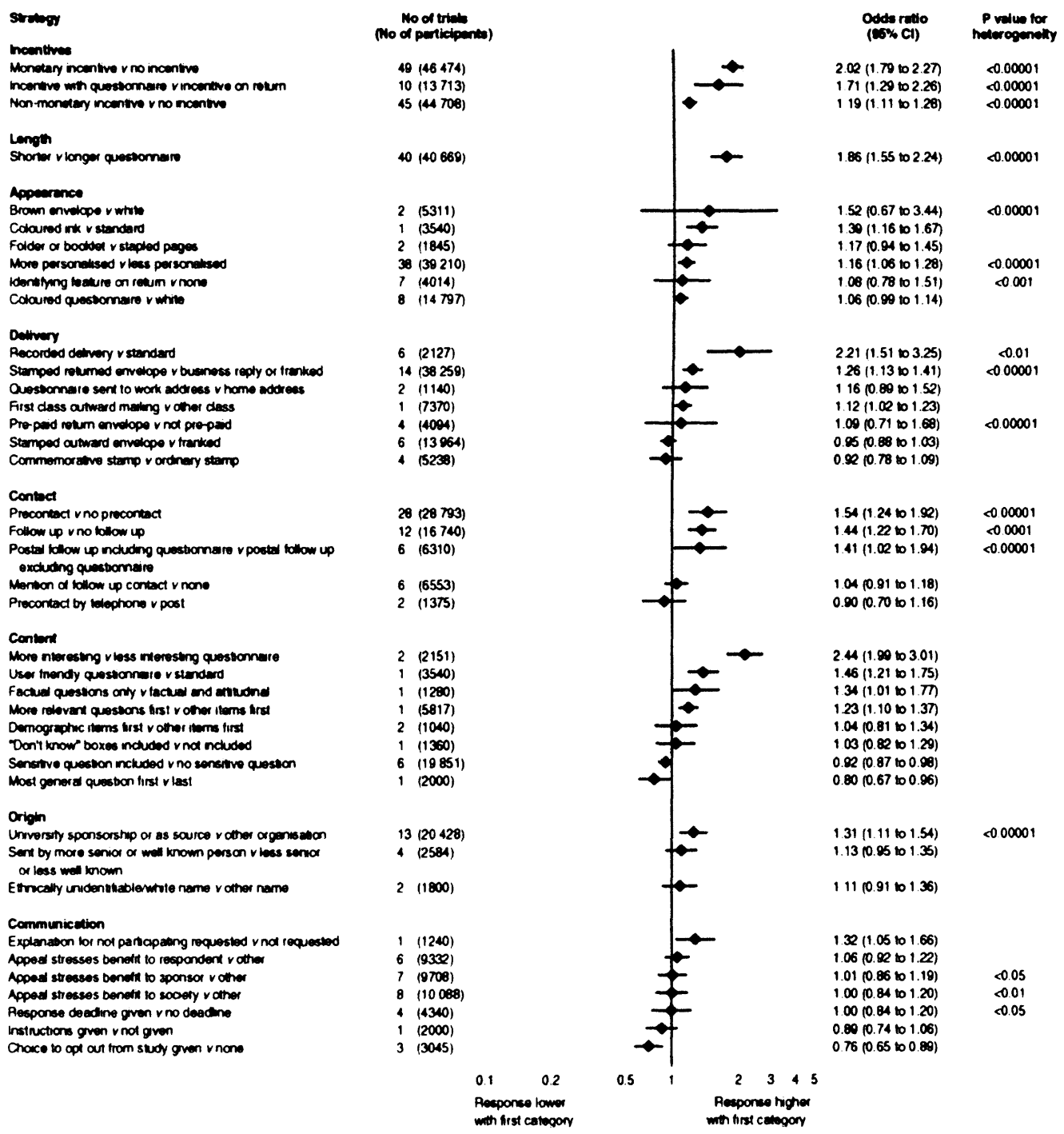
IMD 2004 score = Sum of weighting X dimension scores = (0.225 x Income) + (0.225 x Employment) + (0.135 x Education) + (0.135 x Health) + (0.093 x Housing) + (0.093 Crime)+ (0.093 Environment)

Appendix 3: Age and Ethnic composition of England and Wales and North London. (Office of National Statistics 2004; Office on National Statisitics 2004)

		White (%)	Mixed (%)	Asian (%)	Black (%)	Other (%)	Total (%)
ENGLAND AND WALES							
Males	0-15	4,679,281 (20)	167,766 (52)	333,065 (29)	149,000 (28)	43,029 (21)	5,372,141 (21)
	16-59	13,866,586 (60)	144,649 (44)	717,602 (62)	330,436 (61)	150,677 (73)	15,209,950 (60)
	60+	4,558,423 (20)	12,726 (4)	100,894 (9)	58,594 (11)	13,198 (6)	4,743,835 (19)
	ALL	23,104,290 (100)	325,141 (100)	1,151,561 (100)	538,030 (100)	206,904 (100)	25,325,926 (100)
Females	0-15	4,446,880 (18)	162,837 (48)	318,981 (28)	146,988 (24)	40,909 (17)	5,116,595 (19)
	16-59	14,030,974 (57)	158,613 (47)	714,639 (64)	397,830 (66)	183,646 (77)	15,485,702 (58)
	60+	5,938,722 (24)	14,443 (4)	88,556 (8)	56,729 (9)	15,243 (6)	6,113,693 (23)
	ALL	24,416,576 (100)	335,893 (100)	1,122,176 (100)	601,547 (100)	239,798 (100)	26,715,990 (100)
All	0-15	9,126,161 (19)	330,603 (50)	652,046 (29)	295,988 (26)	83,938 (19)	10,488,736 (20)
	16-59	27,897,560 (59)	303,262 (46)	1,432,241 (63)	728,266 (64)	334,323 (75)	30,695,652 (59)
	60+	10,497,145 (22)	27,169 (4)	189,450 (8)	115,323 (10)	28,441 (6)	10,857,528 (21)
	ALL	47,520,866 (100)	661,034 (100)	2,273,737 (100)	1,139,577 (100)	446,702 (100)	52,041,916 (100)
NORTH LONDON							
Males	0-15	153790 (16)	24073 (47)	65937 (28)	54978 (31)	9378 (20)	308156 (21)
	16-59	635463 (67)	25184 (49)	148794 (63)	102681 (59)	43781 (92)	947012 (65)
	60+	159478 (17)	2376 (5)	22564 (9)	17722 (10)	3110 (7)	205250 (14)
	ALL	948731 (100)	51633 (100)	237295 (100)	175381 (100)	47378 (100)	1460418 (100)

Females	0-15	146770 (15)	23584 (42)	63661 (27)	54369 (26)	8780 (16)	297164 (19)
	16-59	643284 (64)	29773 (53)	151156 (65)	137100 (65)	43781 (78)	1005094 (64)
	60+	215799 (21)	2569 (5)	19286 (8)	18470 (9)	3719 (7)	259843 (17)
	ALL	1005853 (100)	55926 (100)	234103 (100)	209939 (100)	56280 (100)	1562101 (100)
All	0-15	300560 (15)	47657 (44)	129598 (27)	109347 (28)	18158 (18)	605230 (20)
	16-59	1278747 (65)	54957 (51)	299950 (64)	239781 (62)	78671 (76)	1952106 (65)
	60+	375277 (19)	4945 (5)	41850 (9)	36192 (9)	6829 (7)	465093 (15)
	ALL	1954584 (100)	107559 (100)	471398 (100)	385320 (100)	103658 (100)	3022519 (100)

Appendix 4: Forest plot of strategies to improve the response to postal questionnaire. Pooled odds ratios and 95% confidence intervals for the 40 different strategies, divided into eight categories, are illustrated. The combined trials included more than 1000 participants (Edwards et al 2002).



Appendix 5: Template of Monthly surveillance forms from BPSU-like scheme

NLSTEPSS - *N*ORTH *L*ONDON CONVULSIVE *ST*ATUS *EP*ILEPTICUS IN CHILDHOOD *S*URVEILLANCE *S*TUDY

Surveillance Report Card — Month-year

Code [«Source»«Number»]

Dear «Title» «FirstName» «LastName»:

Thank you for assisting in this important study. Please complete this form and return it in the enclosed self addressed envelope.

Indicate below, in the appropriate box, the number of cases of convulsive status epilepticus (SE) aged between 29 days to 15 years you have seen or been informed of this month of February.

If no cases have been seen or have presented to your department, then please tick NO CASES. If there have been cases, please also provide the patient details below.

The working definition of convulsive status epilepticus being used is "A seizure with focal or generalised motor manifestations, or series of such seizures between which consciousness is not regained, which last for 30 minutes or more."

NO CASES ☐	**Cases of status epilepticus** ☐

Patient's Initials	DOB	Registration Number	Date of SE

Yours sincerely,

Richard Chin
Clinical Research Fellow in Paediatric Neurosciences

Rod Scott
Wellcome Advanced Fellow and Lecturer in Paediatric Neurology

Brian Neville
Professor of Paediatric Neurology

Appendix 6: Templates of reminders to non-responders to the Monthly surveillance forms from BPSU-like scheme.

NLSTEPSS - *N*ORTH *L*ONDON CONVULSIVE *ST*ATUS *EP*ILEPTICUS IN CHILDHOOD *S*URVEILLANCE *S*TUDY

Surveillance Report Card — January - 2003

Code [«Source»«Number»]

Dear «Title» «FirstName» «LastName»:

Thank you for assisting in this important study. Unfortunately, we did not receive a reply for January. Please complete this form and return it in the enclosed self addressed envelope.

Indicate below, in the appropriate box, the number of cases of convulsive status epilepticus aged between 29 days to 15 years you have seen or been informed of, for the month of January.

If no cases have been seen or have presented to your department, then please tick NO CASES. If there have been cases, please also provide the patient details below.

The working definition of convulsive status epilepticus being used is "A seizure with focal or generalised motor manifestations, or series of such seizures between which consciousness is not regained, which last for 30 minutes or more."

NO CASES ☐	**Cases of status epilepticus** ☐

Patient's Initials	DOB	Registration Number	Date of SE

Yours sincerely,

Richard Chin
Clinical Research Fellow in Paediatric Neurosciences

Rod Scott
Wellcome Advanced Fellow and Lecturer in Paediatric Neurology

Brian Neville
Professor of Paediatric Neurology

Appendix 7: Information sheets on NLSTEPSS sent to all paediatricians in North London

NLSTEPSS *(North London convulsive STatus EPilepticus in childhood Surveillance Study)*
INFORMATION SHEET for HEALTH PROFESSIONALS

Objective: To determine the incidence, seizure types, treatment strategies, and short term mortality of convulsive status epilepticus in a population of children aged between 29 days to 15 years in North London.

Principal Investigators:

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Dr. Rodney Scott
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Lecturer in Paediatric Neurology
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Neurosciences Unit
The Wolfson Centre
Mecklenburgh Square

Duration: May 2002 for 24 months; extension subject to review

Coverage : London Boroughs of Barnet, , Brent, Camden, City of London, Enfield, Hackney, Hammersmith & Fulham, Haringey, Harrow, Islington, Kensington & Chelsea, Newham, Tower Hamlets, City of Westminster, Waltham Forest.

Case Definition: Report any child aged 29 days to 15 years with convulsive status epilepticus (CSE).

1) **include** :Febrile children with a seizure with focal or generalised motor manifestations, or series of such seizures between which consciousness is not regained, which last for 30 minutes or more.
2) **include**: Afebrile children with a seizure with focal or generalised motor manifestations, or series of such seizures between which consciousness is not regained, which last for 30 minutes or more
3) **exclude**:
   - i) children with non-convulsive status epilepticus
   - ii) children younger than 29 days
   - iii) children 16 years or older
   - iv) children whose seizure is less than 30 minutes

If in doubt please discuss with the Co-ordinating Centre ( )

Reporting instructions:

1. As soon as possible after presentation to your service, please notify by telephone to the ***NLSTEPSS*** Co-ordinating Centre ( ), any child with CSE (febrile or afebrile) according to the case definition above. Please leave your name, telephone number, patient date of birth, patient sex, patient hospital registration number, and the patient's full home postal code.

2. In addition, on the monthly surveillance cards please report all cases of CSE (febrile or afebrile) according to the case definition above which you have seen or made aware of in the last month.

Both methods of reporting are needed for maximum ascertainment. The aim is to be over-inclusive so if in doubt, please discuss with the *NLSTEPSS* Co-ordinating Centre ( ).

Study Design: All children aged 29 days to 15 years with convulsive status epilepticus within the North London region are being notified to the ***NLSTEPSS*** Co-ordinating centre. The patient's postal code will be checked on a database held by the Co-ordinating centre to determine eligibility for the study based on residence in North London. If the patient is eligible you will be contacted by telephone as soon as possible to confirm eligibility. If the patient is not eligible, then no further information will be sought. If the patient is eligible for the study, the patient will be anonymised and a coded study identification number generated by the Co-ordinating centre and provided to the local researcher at your centre. Within five days of notification, a telephone questionnaire will be conducted with a member of the local paediatric team. All the information sought from the reporting local paediatric team will be available from medical records.

The study aims to obtain patient data from medical records and it is not the intention of the Co-ordinating centre to take over the clinical management and investigation of patients by participating centres. Neither is it intended to change the referral system as it currently exists.

Paediatric Intensive Care Consultants will be approached together with all Paediatricians. All Neurophysiology and Accident and Emergency Consultants who help to manage patients from North London will be independently approached regularly for any cases presenting or known to them. Patient officer databases, paediatric admission databases, A&E databases in each participating hospital will also be reviewed.

Ethical Approval : London MREC

Further information available on request or access our web-page under the Neurosciences unit, Institute of Child Health http://www.ich.ucl.ac.uk/nlstepss

Appendix 8: Template of letter publicising and requesting assistance in NLSTEPSS. Letters were sent to all paediatricians in North London.

[Date]

[Name of Doctor]
[Address of Doctor]

Dear [Name of Doctor]

NLSTEPSS *(North London convulsive STatus EPilepticus in childhood Surveillance Study)*

We would like to ask for your assistance in a prospective surveillance study on the epidemiology of status epilepticus in childhood. The study design is similar to that of the British Paediatric Surveillance Unit but will be regional rather than national and will involve 22 centres that provide treatment for children who live in North London.

A Research Collaborative Group has been formed and is made up of Consultants from each of the participating centres. The research will be co-ordinated through the ***NLSTEPSS*** Co-ordinating Centre.

We understand how busy you are and we have kept the information required down to a minimum but are very grateful for your help.

You can help us by :

1) Completing the yellow surveillance card that will be sent to you monthly and

2) To telephone report to the ***NLSTEPSS*** Co-ordinating Centre (
), all cases of convulsive status epilepticus as soon as possible after presentation.

Should you have any questions then you could contact either your local collaborator, or Dr. Richard Chin or Dr. Rodney Scott or Professor Brian Neville. For full contact details please see enclosed ***NLSTEPSS*** Information Sheet.

We have also enclosed a flyer.

The study commencement date is May 1, 2002.

Yours sincerely,

Appendix 9: Questionnaire (Admission Proforma) used in NLSTEPSS

CLERKING PROFORMA for Status Epilepticus in Childhood

Date of completion of Proforma:

Time of completion of Proforma:

Attach label here

Name: _____ Address _____

Hospital Number _____ _____

Date of Birth _____ _____ Post Code _____

Sex _____

Consultant: _____

GP Name: _____

GP Address: _____

GP Telephone: _____

PROBLEM LIST:

History taken from:

Were there any difficulties in obtaining the history? Yes ☐ No☐
If YES, please specify:

1. History of Presenting Complaint
a) Date of status epilepticus (if different):
b) Time of onset of status epilepticus: __ : __ am / pm (From witness)
c) What time was the ambulance called ? __ : __ am / pm N/A ☐ (see ambulance notes)
d) What time did the ambulance arrive to the child? __ : __ am / pm N/A ☐ (see ambulance notes)
a) What time did the ambulance arrive to A&E? __ : __ am / pm N/A ☐ (see ambulance notes)
f) Time of termination of status epilepticus: __ : __ am / pm
g) Total duration of status epilepticus
h) Did the parents think the child was febrile? Yes ☐ No☐ Unsure ☐ If yes, did they measure the temperature? Yes ☐ No☐ What was the temperature recorded?
i) Was the seizure onset Focal ☐ or Generalised ☐
j) Vital Observations on admission GCS Temp Pulse CRT BP RR O_2 Sats (See below)

Eyes Opening			
Score	>1 year	< 1 year	
4	Spontaneously	Spontaneously	
3	To verbal command	To shout	
2	To pain	To pain	
1	No response	No response	
Best Motor Response			
Score	>1 year	< 1 year	
6	Obeys	Spontaneous	
5	Localises pain	Localises pain	
4	Flexion - withdrawal	Flexion – withdrawal	
3	Flexion - abnormal (Decorticate rigidity)	Flexion – abnormal (Decorticate rigidity)	
2	Extension	Extension	
1	No response	No response	
Best Verbal response			
Score	>5 yrs	2-5 yrs	0-23 months
5	Orientated and converses	Appropriate words and phrases	Smiles, coos
4	Disorientated and converses	Inappropriate words	Cries, unconsolable
3	Inappropriate words	Persistent screams or cries	Persistent inappropriate crying/screaming
2	Incomprehensible	Grunts	Grunts or restless
1	Grunts	No response	No response

1. History of Presenting Complaint (Continued)

k) In the space below, please give further details of HPC:

2. TREATMENT OF STATUS EPILEPTICUS

Treatment given for status epilepticus including at home, by the paramedics, and on arrival to hospital: (Please continue on separate sheet if necessary)

Home/paramedics/ hospital	Drug	Dose	Route	Time given (hr : min)	Complications of treatment
For example: Home	Diazepam	5mg	PR	06:15	Nil

3. PERINATAL HISTORY

a) Is this child a: Singleton □ Twin I □ Twin II □ Other□

b) Place of Birth

c) Gestation (in weeks)

d) Type of Delivery Spontaneous Vaginal Delivery □
Other □

If other, please give details

e) Birth Weight

f) Were there any problems during Pregnancy, Labour, Delivery, or the Neonatal period? Yes□ No□ DK□

If yes, please specify :

4. DEVELOPMENT

a)
Were there any parental concerns about any aspect of their child's development prior to this episode of status epilepticus? Yes☐ No☐ DK ☐
If yes, please specify :

b) To the best of the parent's recollection, when were these Milestones achieved:

Social smile at____weeks
First words at _____ months
Walked unaided at____months
Putting words together at _____months

c) If the child is of school age:

- Does the child need special help in school? Yes☐ No☐

- Is the child statemented? Yes☐ No☐

5. PAST MEDICAL HISTORY

a) Has the patient previously been diagnosed with epilepsy or has had previous seizure(s), or has had a "funny turn"? Yes ☐ No ☐ DK☐

If No or Don't Know then please go to Q5 (b)

If the answer is Yes, please continue and specify the following :

i) Age of patient at first seizure/"funny turn":

ii) Cause (if known):

b) Does the child have any other medical illnesses? Yes ☐ No ☐

If Yes, then please specify:

5. PAST MEDICAL HISTORY (Continued)

c) Has the patient previously been admitted to hospital for status epilepticus or any other illnesses? Yes☐ No☐ DK ☐

If Yes, please complete the table below :

Date	Age	Hospital	Duration of admission	Cause (if known)

d) Has the patient previously been investigated for seizures? Yes ☐ No ☐

EEG Yes ☐ No ☐ Date: Normal☐ Abnormal ☐

CT of Brain Yes ☐ No ☐ Date: Normal☐ Abnormal ☐

MRI of Brain Yes ☐ No ☐ Date: Normal☐ Abnormal ☐

If any abnormal, specify hospital where test performed and result:

e) Is the patient currently on any anti-epileptic medication(s) or any other medication? Yes☐ No☐ DK ☐

If the answer is No or Don't Know then please go to Q 5 (f)

If the answer is Yes, please complete the table below:

Medication	Dose and frequency	Dose (mg/kg)

5. PAST MEDICAL HISTORY (Continued)

f)

i) Previous anti-epileptic medications

ii) Please outline any change in medication type/ dosage in the last 2/52

g) Most recent anti-epileptic medication levels and date:

Date	Medication	Level	Normal range

h) Any Drug allergies? Yes☐ No☐

If yes, please specify

i) Is the patient fully immunised for age? Yes☐ No☐

If NO, please specify reason:

j) Please outline any other significant medical history

6. TRAVEL HISTORY

Any recent travel overseas Yes☐ No☐

If yes, please specify

7. FAMILY HISTORY

a) Please draw family tree

b) Is there any consanguinuity? Yes☐ No☐

If YES, please specify

c) Is there a family history of seizures or developmental problems?

Yes ☐ **No** ☐

DK ☐

If YES, please specify:

8. Social History

a) Please outline any significant social history:

b) What ethnic group does the patient belong to?
(Can check nursing notes)

Mixed

White and Black Caribbean ☐
White and Black African ☐

White and Asian ☐

Other - please state ☐

_____

White

British ☐
Irish ☐
Other - please state ☐

_____

Chinese or other Ethnic Group

Chinese ☐
Other - please state ☐

_____

Asian/Asian British

Indian ☐
Pakistani ☐

Bangladeshi ☐

Other - please state ☐

_____

Black/Black British

Caribbean ☐
African ☐
Other - please state ☐

_____

EXAMINATION

9. EXAMINATION WITHIN 30 MINUTES POST TERMINATION OF STATUS			
GCS **Temp** **Pulse** **CRT**	**BP**	**RR**	**O_2 Sats**
Any dysmorphic features?: Yes☐ No☐ Don't Know ☐ If yes, please specify:			
Any birthmarks or congenital abnormalities of the skin or hair? Yes☐ No☐ Don't Know ☐ If yes, please specify:			
Head Circumference: **Weight:** **Height:**	Percentile: Percentile: Percentile:		
Is the head shape normal? Normal ☐ If abnormal, please specify	Abnormal☐	Don't Know☐	
ENT Normal ☐ If abnormal, please specify	Abnormal☐	Don't Know☐	
Cardiovascular system Normal ☐ abnormal, please specify	Abnormal☐	Don't Know☐	
Respiratory system Normal ☐ If abnormal, please specify	Abnormal☐	Don't Know☐	
Abdomen Normal ☐ If abnormal, please specify	Abnormal☐	Don't Know☐	
Genitalia Normal ☐ If abnormal, please specify	Abnormal☐	Don't Know☐	

9. EXAMINATION WITHIN 30 MINUTES POST TERMINATION OF STATUS (CONT'D)

Were you able to see the optic fundi? Yes☐ No☐

If yes, please specify findings:

Neurological examination : Normal ☐ Abnormal☐

If abnormal, please specify abnormality:

10. INVESTIGATIONS & RESULTS			
TESTS	**Y/N**	**DATE**	**RESULTS**

11. OUTCOME		
a) Patient survived?	Yes☐	No☐
b) Patient transferred to PICU? If yes, please specify which PICU:	Yes☐	No☐
Provisional diagnosis:		

Signature of person completing Proforma:
Name of person completing Proforma:
Position of person completing Proforma
Bleep of person completing Proforma

12. DISCHARGE NEUROLOGICAL EXAMINATION FINDINGS		
Did you find any problems with the cranial nerves?	Yes☐	No☐
If *yes*, please give details below		
Did you find any problems with tone, power, coordination, sensation or reflexes in the limbs?	Yes☐	No☐
If *yes*, please give details below		
Were you able to see the optic fundi?	Yes☐	No☐
If yes, please specify findings:		
Any other abnormalities of the nervous system?	Yes☐	No☐
If yes, please specify findings		

Signature of person doing discharge examination:
Name of person doing discharge examination:
Position of person doing discharge examination:
Bleep of person doing discharge examination

Appendix 10: Data collection form for retrospective group in PICU study described in Chapter 7

GOSH PICU Status Epilepticus

Attach label here

2. Name: _____ 3. Post Code_____

4. Date of Birth_____ 5.Sex: M F

6.GOSH Reg Number_____

7.Consultant:_____

8.Referring Hospital_____

9.GP Name:_____

10.GP Address: _____

11.GP Telephone: _____

12.Patient Details - Ethnic Origin of patient

Mixed

1) White and Black Caribbean ☐
2) White and Black African ☐
3) White and Asian ☐
4) Other - please state ☐

_____

White

9) British ☐
10) Irish ☐
11) Other - please state ☐

_____

Chinese or other Ethnic Group

15) Chinese ☐
16) Other - please state ☐

_____

Asian/Asian British

5) Indian ☐
6) Pakistani ☐
7) Bangladeshi ☐
8) Other - please state ☐

_____

Black/Black British

12) Caribbean ☐
13) African ☐
14) Other - please state ☐

_____

STATUS EPILEPTICUS EVENT DETAILS
13. Date of status epilepticus:
14. Time of onset of status epilepticus: _ _ : _ _ am / pm *(From witness)*
15. What time was the ambulance called ? _ _ : _ _ am / pm N/A ☐ *(see ambulance notes)*
16. What time did the ambulance arrive to the child? _ _ : _ _ am / pm N/A ☐ *(see ambulance notes)*
17. What time did the ambulance arrive to A&E? _ _ : _ _ am / pm N/A ☐ *(see ambulance notes)*
18. Time of clinical termination of status epilepticus: _ _ : _ _ am / pm
19. Did the parents think the child was febrile? 1) Y 2) N 3) Unsure/DK 20. If yes, did they measure the temperature? 1) Y 2) N 21. What was the temperature recorded? °C
22. Was the seizure onset 1) Focal ☐ or 2) Generalised ☐
23. Description of SZ:

STATUS EPILEPTICUS EVENT DETAILS - Treatment of SE

24.Treatment given for status epilepticus including at home, by the paramedics, and on arrival to hospital: (Please continue on separate sheet if necessary)

Home/paramedics/ hospital	Drug	Dose	Route	Time given (hr : min)	Complications of treatment
For example: Home	Diazepam	5mg	PR	06:15	Nil

25. Ventilated	**Y/ N**
26. Time of Entubation	_ _ : _ _ am / pm
27. Reason for Ventilation	**1. Safety of transfer** **2. Respiratory insufficiency** a) compromised airway b) decreased resp drive c) sats<95 and/or cap pCO2> 6.5kPa **3. GCS<8** **4. Cause not specified**
28. Child paralysed for Transfer	**Y/N**
29. EEG monitoring for SZ control	**Y/N**
30. If yes, time of Sz termination (based on EEG)	_ _ : _ _ am / pm

Patient Details - PERINATAL HISTORY

Q31.

1) Singleton	2) Twin 1	3) Twin 2	4) Other

32. . Gestation (/40): _____

33. Induced: 1) Yes 2) No 3) Don't Know

34. Type of Delivery :

1) Vaginal 2) Elec C/S 3) Emer C/S 4) Forceps 5) Ventouse

6)Forceps and C/S 7) Ventouse and C/S 8)Forceps and Ventouse 9) Other

35. Birth Weight (in kgs):

36. APGARS: @1 @5 @10

37. **Perinat. Prob's**	1) Yes	2) No	3) Don't Know

38. **If yes to perinatal problems:**

a) **Maternal DM**	1) Yes	2) No	3) Don't Know
b) **Gestational DM**	1) Yes	2) No	3) Don't Know
c) **HPT pre-pregnan**	1) Yes	2) No	3) Don't Know
d) **HPT in pregnancy**	1) Yes	2) No	3) Don't Know
e) **Pre-eclampsia**	1) Yes	2) No	3) Don't Know
f) **Infection**	1) Yes	2) No	3) Don't Know
g) **Social Drugs**	1) Yes	2) No	3) Don't Know
h) **Prem ROM**	1) Yes	2) No	3) Don't Know
i) **Prolong ROM**	1) Yes	2) No	3) Don't Know
j) **Advanced resus**	1) Yes	2) No	3) Don't Know
k) **SCBU**	1) Yes	2) No	3) Don't Know
l) **Ventilated**	1) Yes	2) No	3) Don't Know
m) **Seizures**	1) Yes	2) No	3) Don't Know
n) **HIE**	1) Yes	2) No	3) Don't Know
o) **ICB/IVH**	1) Yes	2) No	3) Don't Know
p) **Hydrocephalus**	1) Yes	2) No	3) Don't Know

Patient Details - Development

39. Any developmental abnormalities? 1) Yes 2) No 3) DK

40. If yes, please specify :

If the child was of school age:

41. Did the child need special help in school? 1) Yes☐ 2) No☐

42. Was the child statemented? 1) Yes☐ 2) No☐

Patient Details - Family &Social History

43. Was there any consanguinuity? 1) Yes☐ 2) No☐

44. If YES, please specify

45. Was there a F/HX of seizures or developmental problems? 1)Y 2) N 3)DK

46. If YES, please specify:

Patient Details - PMH- Previous Sz

47. **Had the patient previously been diagnosed with epilepsy , has had previous seizure(s), or had a "funny turn"?** 1)Y 2) N 3)DK

If the answer is No or Don't Know then please go to **Q62**

If the answer is Yes, please continue and specify the following :

48. Age of patient at first seizure/"funny turn":

49. Cause /diagnosis (if known):

Patient Details - PMH -Past Hospital admissions

50. **Was the patient previously been admitted to hospital for status epilepticus or prolonged febrile convulsion or any other illnesses?** 1)Y 2) N 3)DK

51. If yes, please complete the table below :

Date	Age	Hospital	Duration of admission	Cause (if known)

Patient Details - PMH -Past Hospital admissions

52. Prior to SE, had the patient previously been investigated for seizures? Y N

53. EEG Yes □ No □ Date: Normal□ Abnormal □

54. CT of Brain Yes □ No □ Date: Normal□ Abnormal □

55. MRI of Brain Yes □ No □ Date: Normal□ Abnormal □

56. If any abnormal, specify hospital where test performed and result:

Patient Details - PMH -Maintenance AED's

57. **Was the patient on any anti-epileptic medication(s) or any other medication?** 1)Y 2) N 3)DK

If the answer is No or Don't Know then please go to **Q61**

58. If the answer is Yes, please complete the table below:

Medication	Dose and frequency	Dose (mg/kg)

Patient Details - PMH -Previous AED's

Q59. - Previous medications

Q60 - Please outline any change in medication type or dosage in the last 2/52

Patient Details - PMH -Maintenance AED levels

61. Most recent anti-epileptic medication levels and date:

Date	Medication	Level	Normal range

Patient Details - PMH -Other significant PMH

62. Any other relevant past medical history? Yes☐ No☐ Don't Know ☐

63.If yes, please specify :

EXAMINATION

EVENT EXAMINATION - VITALS ON ADMISSION (Q64-Q70)						
GCS	Temp	Pulse	CRT	BP	RR	O_2 Sats

EVENT EXAMINATION - < 30 MINS POST TERMINATION OF SE (Q70-Q76)			
GCS TempPulse CRT BP RR O_2 Sats			
77.Any dysmorphic features?: 1)Yes☐ 2) No☐ 3) Don't Know ☐ 78.If yes, please specify:			
79.Any birthmarks or congenital abnormalities of skin / hair? 1) Y 2) N 3) DK 80.If yes, please specify:			
81.Head Circumference: **83.Weight:** **85.Height:**		82.Percentile: 84.Percentile: 86.Percentile:	
87. **Lymph nodes** 1) Normal ☐ 2) Abnormal☐ 3) Don't Know☐ 88. If abnormal, please specify			
89. **Is the head shape normal?** 1) Normal ☐ 2) Abnormal☐ 3) Don't Know☐ 90. If abnormal, please specify			
91. **Cardiovascular system** 1) Normal ☐ 2) Abnormal☐ 3) Don't Know☐ 92. If abnormal, please specify			
93. **Respiratory system** 1) Normal ☐ 2) Abnormal☐ 3) Don't Know☐ 94. If abnormal, please specify			
95. **Abdomen** 1) Normal ☐ 2) Abnormal☐ 3) Don't Know☐ 96. If abnormal, please specify			
97. **Genitalia** 1) Normal ☐ 2) Abnormal☐ 3) Don't Know☐ 98. If abnormal, please specify			
99. **Neurological examination** : 1) Normal ☐ 2) Abnormal☐ 100. If abnormal, please specify abnormality:			

PICU COURSE

CVS		
101.	Lowest Systolic BP	
102.	Lowest HR	
103.	Highest HR	
104.	Cardiac Arrest	
105.	Lowest pH (with normal PaCO2)	
106.	Inotropic support needed	Y/N

Respiratory System (Q 107 - 127)									
Time			**PARAMETERS**						
	Min VR	Max VR	Max spont RR	Max MAP	Min PaO2	Min PaO2/ FiO2	Max PaCO2	Max OI	Ventilation Duration
Throughout Admission									
At lowest Vent Rate (VR)	N/A	N/A							N/A
At highest VR	N/A	N/A							N/A

Nervous System		
128.	Lowest GCS	
129.	Fixed dilated pupils	Y/N

Haematological		
130.	Lowest Hb	See Inv Results
131.	Lowest WBC	See Inv Results
132.	Lowest Platelets	See Inv Results

Renal System		
133.	Highest Urea	See Inv Results
134.	Highest Creatinine	See Inv Results
135.	Dialysis	Y/N

EVENT DETAILS - DISCHARGE EXAMINATION FINDINGS
135. Did you find any problems with the cranial nerves? 1) Yes☐ 2) No☐ 136.If *yes*, please give details below
137.Any problems with tone/ power/ coordination/sensation/ reflexes in the limbs? 1) Yes☐ 2) No☐ Q138.If *yes*, please give details below
139.Were you able to see the optic fundi? 1) Yes☐ 2) No☐ 140.If yes, please specify findings:
141.Any other abnormalities of the nervous system ? 1) Yes☐ 2) No☐ 142.If yes, please specify findings

EVENT DETAILS - OUTCOME
143.Patient survived? 1) Yes☐ 2) No☐
144.Provisional diagnosis:

EVENT DETAILS - INVESTIGATIONS			
A) BLOOD	**Y/N**	**Date**	**Results**
145. Full Blood Count			Hb WBC Plt
146. Lowest Hb			
147. Lowest WBC			
148. Lowest Platelets			
149. Differential WBC			Neut Lymp
150. ESR			
151. CRP			
152. Glucose			
153. Urea and Electrolytes			Na K CO2 Urea Creatinine
154. Highest Urea			
155. Highest Creatinine			
156. Calcium			
157. Magnesium			
158. Antiepileptic drug level LMT Carbamazepine Phenytoin Phenobarbitone Propofol Thiopentone Valproate (Others - List names)			
159. Lowest pH (with normal PaCO2)			
160. Lactate			
161. Ammonia			
162. Serum Amino Acids			
163. Blood Virology			
164. Blood Culture			

165. Other Blood tests			
B) CSF (If applicable)			
166. Cell Count			RBC WBC Org
167. Protein, Glucose, lactate			Protein Glucose Lac
168. Culture &S			
169. Virology including HSV, echo, entero, adeno, coxsackie, HHV 6, HHV7			
170. Saved CSF			
171. Other CSF			
EVENT DETAILS - INVESTIGATIONS			
Urine			
172. Organic Acids			
173. Amino Acids			
174. Culture			
175. Dipstix			
176. Other			
Genetics/Imaging/EEG			
177.Chromosomes			
178.Other Genetics			
179.MRI			
180.CT			
181.Cranial U/S			
182.EEG			

183.Other

European Journal of Neurology 2004, **11:** 800–810

CME ARTICLE

A systematic review of the epidemiology of status epilepticus

R. F. M. Chin[a,b], B. G. R. Neville[a] and R. C. Scott[a,c]

ORIGINAL ARTICLE

Meningitis is a common cause of convulsive status epilepticus with fever

R F M Chin, B G R Neville, R C Scott

Arch Dis Child 2005;**90**:66–69. doi: 10.1136/adc.2003.038844

PAPER

Inappropriate emergency management of status epilepticus in children contributes to need for intensive care

R F M Chin, L Verhulst, B G R Neville, M J Peters, R C Scott

J Neurol Neurosurg Psychiatry 2004;**75**:1584–1588. doi: 10.1136/jnnp.2003.032797