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Chylothorax in Infants and Children in the United Kingdom

by

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Thesis for the degree of Doctor of Clinical Practice

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ABSTRACT

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CHYLOTHORAX IN INFANTS AND CHILDREN IN THE UNITED KINGDOM

Caroline Haines

This study was carried out following observation from health professionals in the paediatric intensive care community that the incidence of chylothorax development in infants and children in the United Kingdom was unknown. Furthermore, treatment strategies were based on limited international evidence from single centre, small scale, retrospective cohort studies or case series.

The aim of this study was therefore to determine the size and extent of the problem by establishing the current incidence, patient profile, management strategies and discharge destination or outcome of infants and children who developed a chylothorax in the UK.

Infants and children ≥ 24 weeks gestation to ≤16 years, who developed a chylothorax in the UK were prospectively reported through the British Paediatric Surveillance Unit (BPSU). Clinicians completed a questionnaire on the presentation, diagnosis, management and discharge destination or outcome of these children. Three further additional data sources were accessed to confirm this data.

A total of 219 questionnaires were returned with 173 cases meeting the eligibility criteria for inclusion. The incidence in children in the UK was 1.4 in 100,000 (0.0014%), in infants ≤12 months 16 in 100,000 (0.016%) and for those developing a chylothorax following cardiac surgery it was 3.1% (3,100 in 100,000).

The majority of chylothoraces were reported following cardiac surgery (65.3%). Chylothorax was most frequently confirmed by laboratory verification of triglyceride content of the pleural fluid ≥1.1 mmol/litre (66%). Although a variety of management strategies were employed, treatment with an intercostal pleural catheter (86.5%) and a Medium Chain Triglyceride (MCT) diet (89%) were most commonly reported. The majority of the children had a prolonged hospital stay (median 29.5 days), with a reported mortality of 12.5%.

The results of this study indicate that the development of a chylothorax in infants and children in the UK is not common; although incidence is higher in children having cardiac surgery. The duration of hospital stay is lengthy and therefore the impact on the child, family and hospital resources are significant. Common management strategies exist, but the variation in these and the lack of an outcome based rationale suggest national guidance is required.

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DECLARATION OF AUTHORSHIP

I, Caroline Haines

declare that the thesis entitled

Chylothorax in Infants and Children in the United Kingdom

and the work presented in the thesis is both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- none of this work has been published before submission.

Signed: ……..

Date:……

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Definitions

Ascertainment

The method by which individuals with a trait are selected or discovered by an investigator (Knowles *et al.* 2006).

Ascertainment Bias

The systematic failure to represent equally all classes of cases or people supposed to be represented in a sample. It occurs when false results are produced by non-random sampling and conclusions made about an entire group are based on a distorted or non-typical sample. In research, if ascertainment bias is not accounted for, results can be erroneously attributed to the phenomenon under study rather than to the method of sampling (McCarty *et al.* 1993).

Case-Series Studies

These reports were based on both specific exposure and outcome (i.e. chylothorax in children having cardiac surgery). There was no control or comparison group and therefore calculation of incidence was not possible, the studies only reported a count of cases.

Child or Children

For the purpose of brevity, infants, children and young people included in this study are referred to as child or children throughout. Ages are given where relevant and otherwise refer to those aged ≥ 24 weeks gestation to ≤16 years of age.

Chylothorax

Chylous pleural effusion or chylothorax is defined as the accumulation of chyle-containing lymphatic fluid in the pleural or mediastinal space and usually occurs secondary to disruption of the thoracic duct or derangement of

lymphatic flow within the thorax (Das & Shah 2010;Doerr *et al.* 2005;Suddaby & Schiller 2004). Chyle is classically described as having a white, milky, or opalescent appearance and is composed of fats (phospholipids, cholesterol and triglycerides), proteins (albumin, immunoglobulins and fibrinogen), electrolytes, fat soluble vitamins and lymphocytes (Das & Shah 2010;Doerr *et al.* 2005).

Chylothorax (acquired)

This refers to a chylothorax that occurs after medical or surgical treatment or following trauma. It includes non-traumatic (secondary) forms of chylothorax which result due to obstruction of the thoracic duct, for example by intrathoracic tumours or inflammatory diseases.

Chylothorax (Congenital)

A congenital chylothorax refers to one that occurs as a result of thoracic atresia, or malformation of the lymphatic system, or thoracic duct.

Congenital

A congenital disorder, or congenital disease, refers to a condition existing at or before birth, or one that develops during the first month of life (neonatal disease), regardless of causation.

Incidence

The incidence of a disease is defined as the number of new cases of a disease that occur during a specified period of time in a population at risk for developing the disease (Gordis 2008). In this study it refers to the new cases of chylothorax which occurred within the defined population over a thirteen month period from June 2010 – June 2011.

$$\frac{\text{Number of new cases of a disease occurring in the population during a specified period of time}}{\text{Number of persons at risk of developing the disease during that period of time}}$$

Interventional Cardiology
A sub-specialty of Cardiology that uses intravascular catheter-based techniques with specialized imaging to diagnose and treat cardiac disorders.

Nurse Consultant Role
Nurse consultants are experienced registered nurses, who have specialised in a particular field of healthcare, and were first established in the United Kingdom in 1999. They spend a minimum of 50% of their time working directly with patients, ensuring service users' benefit from expert nursing knowledge and skills. Additionally, the role is responsible for progress in service development, participating and being involved in research and evaluation, and contributing to education, training and development.

Neonatal
Pertaining to the period immediately after birth, in children it refers to the first four weeks of life.

Neonatal Congenital (Primary Diagnosis)
Development of a chylothorax that is thought to be associated with any congenital condition or malformation existing at or before birth e.g. lymphangiectasis, hydrops fetalis, prematurity, Down syndrome or Noonan syndrome.

Neonatal (Other) (Primary Diagnosis)
Development of a chylothorax that is thought to be associated with any disorder, or condition that develops during the first month of life e.g. Persistent pulmonary hypertension of the newborn (PPHN), birth trauma or asphyxia.

Population / Children

The 'population' or reference to 'children' in this study refers to infants and children ≥ 24 weeks gestation to ≤16 years of age, who developed a chylothorax between 1st June 2010 – 30th June 2011, in the United Kingdom (UK).

Retrospective Cohort Studies

These reports were based on children sampled on the basis of exposure (i.e. having cardiac surgery) and then assessed for the occurrence of a specified outcome (i.e. chylothorax). Comparison with those who did not develop the condition was possible and therefore incidence rates were presented.

Triangulation

Triangulation is an approach to research that uses a combination of more than two research strategies or methods in a single investigation (Tappen 2011). This approach can help facilitate the validation of data and findings.

Abbreviations

ASD	Atrial septal defect
AV	Atrioventricular
AVSD	Atrioventricular septal defect
BPSU	British Paediatric Surveillance Unit
CCAD	Congenital Cardiac Audit Database
CoA	Coarctation of the aorta
DH	Department of Health
g/l	Grams per litre
HES	Hospital Episode Statistics
ICD	International Classification of Diseases
IQR	Interquartile range
IV	Intravenous
Kg	Kilogram
LCT	Long chain triglyceride
MCT	Medium chain triglyceride
mmol/L	Millimols per Litre
NHS	National Health Service
OCT	Octreotide
ONS	Office for National Statistics
PAIVS	Pulmonary atresia with intact ventricular septum,
PAVSD	Pulmonary atresia with ventricular septal defect,
PD	Pleural Drain
PDA	Patent ductus arteriosus
PICANet	Paediatric Intensive Care Audit Network
PS	Pulmonary stenosis
RVOT	Right ventricular outflow tract
SHA	Strategic Health Authority
SPSS®	Statistical Package for the Social Sciences
SST	Somatostatin
TAPVD	Total anomalous pulmonary venous drainage
TCPC	Total cavopulmonary connection / Fontan,
TGA	Transposition of the great arteries
TOF	Tetralogy of Fallot
TPN	Total Parenteral Nutrition

Tx	Treatment
UK	United Kingdom
VATS	Video-assist thoracoscopic surgery
vs.	versus
VSD	Ventricular septal defect
WHO	World Health Organisation

1. Introduction

1.1 Introduction to the study

Over the past decade, with the availability of increased technology, improved drug therapies and greater medical and nursing knowledge and expertise, mortality rates within paediatric and neonatal intensive care specialities have fallen (PICANet 2012). Health professionals are now focusing their knowledge and skills on improving children's outcomes by optimising effective management strategies and wherever possible preventing significant morbidity, through complications such as chylothorax. The co-morbidity of chylothorax is a condition some children develop following a primary illness, injury, congenital abnormality or surgery; however suggested management strategies vary and the evidence base to the treatments prescribed and administered appears poor.

Those children who develop chylothorax in paediatric intensive care whilst recovering from cardiac surgery are exposed to repeated painful procedures, multiple drug therapies, immobility, weight loss due to dietary changes and an extended stay in this environment, all of which can have a detrimental impact on their recovery and an emotional and developmental impact on both them and their family (Colville 2008;Colville *et al.* 2009;Rennick & Rashotte 2009). Whilst there is substantial evidence in the literature regarding the impact an extended stay in intensive care can have on the child and their family (Colville 2008;Colville *et al.* 2009;Rennick & Rashotte 2009), the increasing demand being placed on these acute beds (Pearson *et al.* 2012) and the considerable cost a lengthy stay in this environment generates (Chalom *et al.* 1999), none specifically discusses or considers chylothorax.

Following an initial review of the literature little evidence was available regarding the incidence of chylothorax development in children, the optimal care these individuals should receive or their hospital discharge outcome. There was therefore a possibility that the care these children were receiving and the information families were being given, may not have been optimal.

1.2 Content of the thesis

To address the lack of evidence and in order to develop and improve the care for children who develop a chylothorax, this thesis investigates and reports on the incidence and current clinical care and related outcomes for children who develop a chylothorax in the UK. An observational, descriptive surveillance study of this under-researched area of clinical practice was undertaken.

In Chapter Two, the literature relating to chylothorax in children is presented. A review of the evidence that focused on incidence, associated conditions, diagnostic testing for chylothorax and existing treatment and management strategies are provided. The study design and methods are described in Chapter Three and the results are presented in Chapter Four which for clarity focus around the research questions. The results are discussed in Chapter Five, giving attention to the limitations of the study. Conclusions, implications for practice and service delivery and recommendations for further research are provided in Chapter Six.

1.3 Conduct of the study

Planning and preparation for this research began in October 2008. The study was approved by the Central London Research Ethics Committee (REC) 2 reference number 10/H0713/27 and the National Information Governance Board (NIGB) ECC/BPSU 3-02(FT) in April 2010. Data collection commenced in June 2010 and continued for thirteen months. Sponsorship was agreed locally by the host Trust Research and Development Department.

2. Literature review

2.1 Introduction

This study focuses on a clinical condition known as chylothorax, a rare but significant disorder occurring in children, most notably evident in the neonatal period, or following cardiothoracic surgery. The medical literature and anecdotal evidence suggest that infants and children who develop this condition are most commonly managed in paediatric or neonatal intensive care units; however the incidence of the condition and currently prescribed and administered treatment options are based largely on limited evidence and vary across centres internationally. These limitations resulted in concerns from health professionals within the United Kingdome (UK) paediatric intensive care community that the extent of the problem, the management strategies provided, length of hospital stay and hospital discharge outcome for these children were unknown and that consequently, the care provided could be suboptimal. To establish the validity of these concerns it was necessary to determine the size and extent of the problem and establish a better understanding of current treatment practices and discharge destination or outcomes for these children.

The following review of the literature therefore provides an overview of the current evidence available on chylothorax development in children (subsections 2.2 – 2.8).

2.2 Background - Development of a chylothorax in infants and children

Chylothorax is an accumulation of chylous lymphatic fluid which develops within the space between the visceral and parietal pleura, and occurs as a result of a congenital malformation, injury or obstruction to the lymphatic system (McGrath *et al.* 2010). Chyle is a milky white fluid formed in the small intestine during digestion of fatty foods, consisting of lymphatic fluid and lipoproteins (fats and proteins) (McGrath *et al.* 2010). It is one of four fluids

which can accumulate within the pleural space, causing symptoms of dyspnoea and increased work of breathing which can result in hypoxia (Allen *et al.* 1991;Caserio *et al.* 2010). Chylomicrons are lipoproteins, which consist mainly of triglycerides (85%-92%), and carry dietary lipids from the intestines to the rest of the body. Chyle is transported around the body via lymphatic vessels draining into the thoracic duct on the left side of the body. This transportation of chyle facilitates the movement of fats from the digestive system to other bodily tissues where they can either be absorbed or metabolised.

Damage to the lymphatic system can occur congenitally, as a result of abnormal development, or as a result of direct injury or damage to the thoracic duct by rupture, laceration, tear or compression (Abreu *et al.* 2004;Beghetti *et al.* 2000;Buttiker *et al.* 1999;Romero 2000), thrombosis or high superior vena cava venous pressure (Beghetti *et al.* 2000). In children, development of a chylothorax has been associated with a variety of congenital malformations (including Noonan syndrome and Down syndrome), congenital lymphangiectasis, tracheoesophageal fistula, thoracic duct hypoplasia, tumour growth, thoracic and/or cardiac surgery and trauma (Doerr *et al.* 2005). These children often require regular and repetitive hospital visits necessitating varied interventional treatments to support their condition and optimise their quality of life. Chylothorax can potentially be a life-threatening disorder (Soto-Martinez & Massie 2009) with metabolic, immunologic or nutritional sequelae. In a group of children who are already potential high service users, these complications can contribute to an increase in the resources required to care for them and add to the financial burden placed on the health service.

Some authors imply these children too frequently feature in the caseload of neonatal and paediatric intensive care units, where treatments appear to be based largely on limited evidence with considerable variability across centres (Beghetti *et al.* 2000;Chan *et al.* 2005). For children being cared for in intensive care environments, studies have shown that the development of a chylothorax can compromise recovery and further extend their stay in an environment where they may be exposed to frightening sights and sounds and

where a high nurse:patient staffing ratio is required. There is often a necessity for additional costly invasive treatment strategies to treat the chylothorax which can further prolong the child's recovery and hospital stay (Beghetti *et al.* 2000;Chan *et al.* 2005;Landvoigt & Mullett 2006). Chylothorax complications can all significantly impact on the cost to the health service, quite apart from exposing these children to a substantially higher risk of additional morbidities, including infection and pain from intercostal pleural catheter (chest drain) and intravenous cannula insertions, reactions to prescribed drug therapies (Beghetti *et al.* 2000) and weight loss from dietary restrictions. A prolonged hospital stay, including the extended period in an intensive care environment, may impact upon both the physiological and psychological well-being of the child and their family, potentially leading to regression in the child's physical development and fear of abandonment (Colville 2008;Rennick & Rashotte 2009) and parental stress, anxiety, depression, marital disharmony and anger (Colville *et al.* 2009).

A review and analysis of the available evidence was therefore undertaken to establish the scale of the problem and to gain a better understanding of current treatment and management practices together with the discharge destination and outcomes for those children who developed a chylothorax.

2.3 Literature review search strategy

A review of studies published in the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane library), MEDLINE, CINAHL, BNI and EMBASE databases was undertaken for the period between January 1990 and May 2013. Additional consideration was given to seminal work published prior to this date and referenced within the reviewed papers. The majority of studies published prior to 1990 relating to paediatric chylothorax are limited to single patient case reports from individual centres. Indeed, the majority of these studies are linked to infants and children who developed a chylothorax either in the neonatal period or following cardiac surgery. In both neonatal and paediatric cardiac care, treatment and management strategies have evolved significantly, with practices prior to 1990 being superseded by more advanced techniques.

An initial literature search was undertaken in June 2009 across all eight databases MEDLINE, CINAHL, EMBASE, BNI, AMED, HEALTH BUSINESS ELITE, HMIC and PsychINFO. The latter four databases were included in this search to review the likelihood of any papers focusing on health administration, management, pharmacology or psychological aspects of chylothorax care in children being published in journals held within these databases. No relevant papers were located (Appendix 1); hence these databases were not included in subsequent searches. The refined database search was repeated in June 2010 and March 2012. Following the review in March 2012 a monthly 'search alert' was programmed to allow for the identification of newly published papers of potential relevance to the study. Each of the above databases was searched separately in order to use a combination of key word and subject heading searches to ensure that all relevant papers were identified.

The literature search included the following free-text and truncated terms: Chylothorax, pleural effusion, lymphangioleiomyomatosis, chylous ascites, chyle, chyl*, thoracic duct, lymphatic disease, lymphatic abnormalities or lymphangioma, cystic, or lymphatic system, somatostatin and octreotide (Appendix 2). To optimise the literature search further and dependent on the structure of the database, some search terms were used in combination and some were refined through the thesaurus mapping function. All database searches were refined further by applying 'age limits' to the search strategy.

Non-English language papers were not included in the study, although consideration was given to foreign studies that had abstracts written in English. Unfortunately resources were not available for translation of papers. However, no non-English language study was referred to in any seminal paper accessed.

In total 379 relevant publications focusing on the development of a chylothorax in children were retrieved and stored in a reference manager database. There was a dearth of high quality studies with one systematic

review (Roehr *et al.* 2006), one literature review (Helin *et al.* 2006), one Cochrane Review (Das & Shah 2010), and one evidence based treatment algorithm (Panthongviriyakul & Bines 2008) identified. Additionally there were three multi-centre case-series studies (Al-Tawil *et al.* 2000;Rocha *et al.* 2006;Tazelaar *et al.* 1993). The majority of articles published were single centre, small scale retrospective cohort studies or single centre case-series reports with most focusing upon the management strategies used to treat these children.

2.4 The current reported incidence of chylothorax in infants and children

The true incidence of chylothorax development children was unknown, with current knowledge being based upon a number of small scale retrospective cohort studies (Beghetti *et al.* 2000;Bond *et al.* 1993;Cannizzaro *et al.* 2006;Katanyuwong *et al.* 2009;Milonakis *et al.* 2009;Nguyen *et al.* 1995), a multi-centre database cohort study (Mery *et al.* 2013) and two case-series reports (Biewer *et al.* 2010;Sersar 2011).

To date, reported chylothorax incidence children has focused on those developing the condition following cardiac surgery and has ranged from 0.5% - 9.2% per centre. These figures are based on the number of chylothorax cases occurring in each research study period, relative to the number of cardio-thoracic surgical procedures undertaken in the same time frame (Table 2-1, Table 2-2 and Table 2-3). The average incidence is 3.2% (3,200 in 100,000), with a median of 2.2% (2,200 in 100,000).

Over the past thirteen years incidence rates have increased from a mean of 1.4% prior to 2000 (range 0.5%-2.5%), to a mean of 4.1% (range 0.89%-9.2%) in children who have had cardiothoracic surgery. Chylothorax prevalence data published by Chan *et al*. (2006) confirms this increase, demonstrating a chylothorax rate of 0.45% between 1981 and 1999, increasing to 2.27% between 2000 and 2004 (Table 2-4). These results are from a small single

centre retrospective cohort study over a 23 year period, which identified 51/5995 children who developed a chylothorax following surgery for a congenital cardiac defect. This centre operated on 260 children each year, a small number in comparison to current UK tertiary centres who currently operate on between 300 and 700 children annually (NICOR 2013). Nonetheless, the increase in incidence and prevalence are likely to be reflective of the improved survival rates of children with cardiac defects. These improvements are associated with increased expertise over the past 20 years in advances in cardiac surgical correction techniques and progress in both technological and pharmaceutical developments. However, whilst cardiac surgical mortality rates have decreased, complications and morbidities, including chylothorax, are not uncommon.

A higher incidence of chylothorax has been observed in children undergoing more complex cardiac procedures, including heart transplantation, Tetralogy of Fallot repair and Fontan procedures (Mery *et al.* 2013). These particular procedures substantially alter the child's haemodynamic state which may result in elevating the superior vena cava pressure, causing a build-up of pressure in the thoracic duct and resulting in increased chyle loss (Chan *et al.* 2006;Kazanci *et al.* 2013;Milonakis *et al.* 2009;Nguyen *et al.* 1995).

Biewer *et al's* (2010) study of children following cardiac surgery identified the highest published incidence rate of 9.2% (n=26), offering the reason that their population may have differed from other studies, with their infants suffering damage to the minor chylous vessels, lymphatic congestion, central vein thrombosis and the need for secondary chest closure. However, when reviewing additional literature it is clear these associated complications are not unique to this study, as all had previously been well documented by others as having links with chylothorax development (Al-Zubairy & Al-Jazairi 2003;Berkenbosch *et al.* 2003;Milonakis *et al.* 2009;Pratap *et al.* 2001). Furthermore, there was no obvious difference in Biewer *et al's* (2010) population when comparing demographic or surgical procedure data with the other studies. With such a small sample and without greater detail on the

treatment and management practices offered within the centre, there can be little confidence in this higher reported incidence.

When attempting to compare the studies that reported on the incidence of chylothorax, the process is confounded by a lack of specific and comparable information. Differing classifications and terms are used for similar cardiac surgical conditions and/or techniques, poor information is available on the stage of a repair if the condition requires multiple surgical procedures, and there is a lack of clarity regarding the definitions used for the denominator of 'total cardiac operations or procedures' in each centre. Sersar's (2011) case-series report does not refer to any denominator figure or comparison group(s), hence the accuracy of his reported incidence rate of 6% is unknown. Conversely, Cormack *et al's* (2004) cohort study identifies the denominator as 'cardiothoracic surgical procedures in children ≤10 years of age', whilst Chan *et al*. (2005) had a numerator of 'all children under the age of 18 years diagnosed with chylothorax after cardiothoracic surgery', with a denominator of all infants and children who had cardiothoracic surgery in their centre over the study period. This information helps clarify the population their incidence refers to, however there is still insufficient information regarding whether these chylothorax cases developed following an open or closed cardiac surgical procedure, or included interventional cardiological procedures such as cardiac catheterization. The former procedures involve surgical techniques in the vicinity of the thoracic duct, damage to which has been identified as having an increased link with chylothorax development (Beghetti *et al.* 2000). Other studies did not state the age ranges included in the denominator, nor which surgical procedures were included, i.e. open or closed cardiac surgical cases and/or interventional cardiac surgical cases. No centre discusses the length of time following cardiac surgery children were observed for the development of a chylothorax and there is varied information provided on how cases were identified for inclusion in the study. Most children had their health record(s) reviewed, some of whom had been identified as developing a chylothorax via a coding system within their department or the hospitals data collection system (Tables1-4). However for others, it is not stated how they were recruited to the study, or how many case notes were reviewed in an attempt to identify all chylothorax cases in their centre. This lack of detail raises questions over case

identification completeness and accuracy and therefore the trustworthiness of the reported incidence.

An additional consideration in this group of children, and only acknowledged by Chan *et al.* (2005) and Mery *et al.* (2013), was the number of cardiac surgeons operating on the infants and children during each individual study period. Chan *et al.* (2005) identifies that they had three surgeons operating during their study, with incidence data for chylothorax varying between each, and reported as 2.8%, 4.3% and 5.8%. Information is not provided on the surgical procedures undertaken by the three surgeons and therefore it is not possible to identify if those with a higher incidence of chylothorax had undertaken more of the corrective surgical procedures that have an increased link with the condition. Mery *et al's* (2013) conference abstract is limited, but reports no connection between chylothorax development and the surgical procedure or volume of work undertaken by each surgeon.

Only Mery *et al's* (2013) database study is multi-centred, although no reference is made to the number of institutions submitting data. No other study discussed or calculated the chylothorax incidence beyond their reporting centre and/or made any reference to national population or sub-population data figures.

Two studies reported on the incidence of congenital chylothorax development in neonates (Caserio *et al.* 2010;Rocha *et al.* 2006) (Table 2-5). Rocha *et al's* (2006) study across six centres in northern Portugal reported an incidence of 1:8,600 deliveries (0.01%). Again however, no reference is made to wider national data comparisons, nor information provided on health service practices within this country. Caserio *et al.* (2010) reported an incidence of 32/106,237 births (0.03%) in their single centre review of congenital chylothorax over a 16 year period and referred to a prevalence reported by (van Straaten *et al.* 1993) of 1/10,000-15,000 births (0.01-0.007%). Neither study provided any incidence data on acquired chylothorax in neonates.

Following a review of the incidence data on chylothorax development in children, it is evident that more information is available on the incidence after cardiac surgery than within any other clinical group, although the true incidence in children in the wider population remains unclear. Whilst there are some useful, informative single and multi-centre cohort studies providing a selective insight into incidence rates, the frequency of the development of a chylothorax and the conditions associated with this are unknown.

A national, multi-centre surveillance study to identify and describe the true incidence and characteristics of this patient population is required to clarify these questions and elucidate the implications for children's care, and service planning and delivery.

Table 2-1 Single-centre, small scale retrospective cohort studies reporting chylothorax incidence following cardiac surgery

Reference	Research question	Method	Incidence – %	Research review / quality
(Higgins & Mulder 1971). California, USA	To review the incidence, modes of therapy and morbidity associated with treatments for chylothorax following congenital cardiac surgery	• Case note review (not stated how cases identified) • Study period 1961 – 1969	• 0.5% (n=6/1118 paediatric intra-thoracic cardiovascular operations) • 1.1% (n=6/532 paediatric congenital cardiac surgical operations)	• Country – USA • Small population. • Age range: 3 mths – 16 yrs • 8 yr data collection period • Study undertaken approx. 50 yrs ago. Paediatric cardiac techniques now more diverse and complex.
(Allen *et al.* 1991). Ohio, USA	To review the nutritional and infectious complications of post – operative chylothorax in children	• Case note review, of those with a discharge diagnosis of chylothorax • Study period 1979 – 1987	• 1.0% (n=18/1713 paediatric cardiac surgical procedures)	• Country – USA • Small population. • Age range: 1 mths – 9yrs • 8 yr data collection period
(Le *et al.* 1991). Geneva, Switzerland	To establish criteria of severity and prognosis of chylothorax as well as guidelines for management	• Case note review (not stated how cases identified) • Study period 1983 – 1989	• 1.9% (n=24/1264 paediatric intra-thoracic procedures)	• Country – Switzerland • Small population. • Age range of those identified: 2 mths – 11yrs • 7 yr data collection period

Reference	Research question	Method	Incidence – %	Research review / quality
(Nguyen *et al.* 1995). Montreal, Canada	To assess the efficacy of two non-operative treatment strategies	• Case note review (not stated how cases were identified) • Study period 1984 – 1993	• 1.5% (n=25/1605 paediatric cardiothoracic procedures)	• Country – Canada • Small population. • Age range: 2 mths – 11yrs • 10 yr data collection period
(Beghetti *et al.* 2000). Geneva, Switzerland	To assess the incidence and aetiology of chylothorax and to assess the centres therapeutic management approach	• Database search for a diagnosis of chylothorax, then a case note review • Study period 1985 – 1996	• 2.5% (n=46/1842 paediatric cardiothoracic surgical procedures)	• Country – Switzerland • Small population. • Age range: 0-16yrs (Median 1.65 yrs) • 12 yr data collection period
(Cormack *et al.* 2004). Auckland, New Zealand	The management of Monogen enteral formula for the management of paediatric post-operative chylothorax	• Database search and dietetic record search for diagnostic code of chylothorax, then case note review • Study period 1999 – 2001	• 4.7% (n=25/535 paediatric cardiac surgical procedures)	• Country – New Zealand • Small population. • Age range: 0-10yrs • 2 yr data collection period
(Chan *et al.* 2005). Toronto, Canada	To determine the incidence, risk factors and outcomes for chylothorax in children undergoing cardiothoracic surgery	• Database search for a diagnosis of chylothorax, then case note review • Study period 2000 – 2002	• 3.8% (n=48/1257 paediatric cardiothoracic surgical procedures)	• Country – Canada • Small population. • Age range: 0-18yrs • 28 mth data collection period

Reference	Research question	Method	Incidence – %	Research review / quality
(Densupsoontorn *et al.* 2005). Bangkok, Thailand	To report on the incidence, aetiology, therapeutic management strategies and outcomes of children diagnosed with a chylothorax or chyloperitoneum	• Case note review (not stated how cases were identified) • Study period 1997 – 2003	• 0.89% (n=15/1683 paediatric cardiothoracic surgical procedures & chylo-pericardium)	• Country – Thailand • Small population. • Age range: 11days-14yrs • 6 yr data collection period
(Cannizzaro *et al.* 2006). Zurich, Switzerland	To analyse the success rate of somatostatin in children with persistent chylothorax who failed dietary treatment options	• Database search for a diagnosis of chylothorax, then case note review • Study period 2000 – 2004	• 6.7% (n=76/1130 paediatric cardiac surgical procedures)	• Country – Switzerland • Small population. • Age range: 1-302days • 5 yr data collection period
(Katanyuwong *et al.* 2009). Rochester, USA	To determine the incidence and outcomes of post-operative chylous pleural effusion and the efficacy of pleurodesis for its management after congenital heart surgery	• Database search for a diagnosis of chylothorax , then case note review • Study period 2000 – 2004	• 1.6% (n=19/1166 paediatric cardiac surgical operations)	• Country – USA • Small population. • Age range: 0-18 yrs • 5.5 yr data collection period
(Milonakis *et al.* 2009). Athens, Greece	To explore the aetiology and present the centres experience with the management of chylothorax following paediatric heart surgery	• Case note review (not stated how cases were identified) • Study period 1997 – 2006	• 1.35% (n=18/1341 paediatric cardiac surgical procedures)	• Country – Greece • Small population. • Age range: 5mths – 5.6yrs • 9 yr data collection period

Reference	Research question	Method	Incidence – %	Research review / quality
(Biewer *et al.* 2010). Nuremberg, Germany	To analyse the risk factors for chylothorax in infants after congenital heart surgery and the efficacy of median chain triglyceride diet (MCT)	• Database search for a diagnosis of chylothorax, then case note review • Study period 2000 – 2006	• 9.2% (n=26/282 paediatric cardiac surgical procedures)	• Country – Germany • Small population. • Infants only • 6 yr data collection period
(Sandra *et al.* 2011). London, UK	To review the aetiology, clinical presentation and outcomes of children who developed a chylothorax after congenital heart disease surgery (Conference abstract only available)	• Database search for a diagnosis of chylothorax, then case note review • Study period 2005–2009	• 2.7% (n=49/1795 paediatric cardio thoracic surgical procedures)	• Country – UK • Small population. • Neonates only • 4 yr data collection period

Table 2-2 Multi-centre, large, retrospective cohort study reporting chylothorax incidence following cardiac surgery

Reference	Research question	Method	Incidence - %	Research review / quality
(Mery *et al.* 2013), Texas, USA	To determine the incidence of chylothorax in children after congenital cardiac surgery or heart transplantation; to determine the associated factors and treatment strategies. (Conference abstract only available)	• Multi-centre database search • It is unclear how many institutions inputted into the database, or what the search terms were. • Study period 2004-2011	• 2.8% (n=2205/77,777 paediatric congenital cardiac surgery or heart transplant)	• Country – USA • Large population • Children <18years • 8 yr data collection period

Table 2-3 Single-centre, retrospective case-series review reporting chylothorax incidence following cardiac surgery

Reference	Research question	Method	Incidence - %	Research review / quality
(Sersar 2011). Jeddah, Saudi Arabia	To establish the predictors of prolonged drainage of chylothorax after cardiac surgery	• Case note review (not stated how cases were identified) • Study period 2007 – 2010	• 6% (n=52), denominator estimated as not given)	• Country – Saudi Arabia • Small population. • Age range: 1mths-60yrs (Mean 30 mths) • 3.9 yr data collection period

Table 2-4 Single centre, small scale, retrospective cohort study reporting chylothorax prevalence following cardiac surgery

Reference	Research question	Method	Prevalence – %	Research review / quality
(Chan *et al.* 2006). Hong Kong, China	To review the centres experience in the management of chylothorax in children following congenital heart surgery	• Database identified – (not stated how), then case note review. • Study period 1981 – 2004	• 0.85% (n=51/5995 paediatric cardiac surgical procedures) • 0.45% between 1981 – 1999. (21/ 4631 cases) • 2.27% between 2000 –2004 (31/1364 cases)	• Country – China • Small population. • Age range: 4 days-19.6 yrs (Median 11 mths) • 23 yr data collection period

Table 2-5 Small scale, retrospective cohort studies reporting chylothorax incidence within pleural effusions in neonates

Reference	Research question	Method	Incidence – %	Research review / quality
(Rocha *et al.* 2006). Northern Portugal	To accurately determine the causes and prognostic significance of pleural effusions in a population of high-risk neonates	• Case note review (not stated how cases were identified) • Study period 1997 – 2004	• n=62 • 1:8,600 deliveries = 0.01% of deliveries	• Country – Portugal – Multi centre – 6 centres. • Small sample size. • All neonates or pre-term infants. • 7 yr data collection period
(Caserio *et al.* 2010). Madrid, Spain	To analyse the pre and post natal features of congenital chylothorax and the outcomes including mid-term follow-up	• Database search for a diagnosis of congenital chylothorax, then case note review. • Study period 1990-2006	• 0.03% (n=32/106,273 births)	• Country – Spain. Single Centre • Small population. • Neonates only • 16 yr data collection period

2.5 The challenges of identifying and diagnosing a chylothorax

Suspecting and confirming chylothorax in a child is dependent upon their underlying condition and presenting signs and symptoms. Neonates born with, or who experience extensive pleural effusions following their birth, or those who have a lymphatic system malformation, appear to be at greater risk of chylothorax development (Beghetti *et al.* 2000;Rocha 2007). Similarly, those children who have had cardiothoracic surgery or who suffer thoracic trauma, or develop a mediastinal or thoracic mass also seem to have a higher risk of developing this condition (Beghetti *et al.* 2000;Cannizzaro *et al.* 2006). Clinicians therefore require greater vigilance and consideration of these children with regard to their potential increase likelihood of chylothorax development.

Diagnosing a chylothorax can prove challenging and whilst a chest x-ray may confirm fluid in the pleura (pleural effusion), causing the child to experience dyspnoea and an increased work of breathing (Allen *et al.* 1991;Caserio *et al.* 2010), it does not provide a definitive clinical diagnosis of chylothorax, as the pleural effusion may instead be the accumulation of blood, empyema or serous fluid (Shih *et al.* 2011). Children who have had placement of a intercostal pleural catheter (chest drain) following cardiothoracic surgery or trauma are less likely to experience the added complications of increased work of breathing or hypoxia due to fluid accumulation with the pleural space, as any fluid will drain out via the intercostal catheter. Earlier recognition of a potential chylothorax is also possible if an intercostal catheter is in situ, as there is an increased ability to see the typically milky coloured fluid draining from the thorax.

However, whilst this milky coloured, non-clotting fluid is typical of chyle, it does not provide sufficient evidence to diagnose the condition (McGrath *et al.* 2010). If the child has not been fed or there has been a reduction in fat intake, the child may still have a chylothorax, but the fluid may be clear due to the absence of lipids (Beghetti *et al.* 2000). Alternatively, it may appear opaque

and turbid with an empyema, or when a chronic pleural effusion with a high concentration of cholesterol, but no triglycerides or chylomicrons present exists (psuedochylothorax) (McGrath *et al.* 2010). Indeed Buttiker *et al.* (1999) found that two out of their ten control patients without a chylothorax had turbid effusions, although the triglyceride content of their pleural fluid (a diagnostic indication of a chylothorax) was low, 0.12 mmol/L and 0.50 mmol/L respectively, highlighting the concern that this milky appearance is misleading serving only as a suggestion that further investigations may be warranted rather than proof that the effusion is chylous.

The gold standard test for chylothorax confirmation is cytological analysis of the pleural fluid stained with Sudan 111, a fat soluble dye used to identify the presence of chylomicrons. This test provides sensitivity, (correctly identifying those children with a chylothorax), but not specificity (correctly identifying those children without a chylothorax) (Lalkhen & McCluskey 2008), and therefore further lipoprotein analysis demonstrating chylomicron values is recommended (McGrath *et al.* 2010;Staats *et al.* 1980). Both these tests can prove costly with analysis equipment not always being available, hence institutions may rely more on the measurement of pleural fluid triglyceride levels. Staat *et al.* suggested criteria for this biochemical diagnosis of chylothorax in 1980. Although his three-year study of 141 patients primarily focused on adults, he identified triglyceride levels which could distinguish chylous effusions from non-chylous effusion at values ≥1.1mmol/L, with inconclusive cases of chylothorax being those with triglyceride values between 0.5 - 1.1 mmol/L, where he advised further lipoprotein analysis. These characteristics and the biochemical composition of chyle can be seen in Table 2-6 (Soto-Martinez & Massie 2009).

It was evident in many key studies reporting on children who developed chylothorax that most institutions use the more readily available and economical, biochemical diagnosis for the confirmation of chylothorax, using triglyceride concentration levels in the fluid of ≥1.1 mmol/L as confirmation. (Buttiker *et al.* 1999;Helin *et al.* 2006;Rocha *et al.* 2006;Rocha 2007). However, others simply relied on the child's clinical history and presentation

and the visual milky colour of the pleural fluid. The variation in how clinicians confirmed the diagnosis potentially impacts on the accuracy of the reported incidence data and the timely prescription and delivery of optimal management strategies for these children. Additionally it highlights variations in clinical practice between institutions depending upon the biochemical analysis equipment available and the preferences of individual clinicians. This poor clarity and option for individual and institutional variation in how chylothorax is confirmed could lead to inaccurate diagnosis and treatment, prolonged length of hospital stay and increased discomfort for the child.

Table 2-6 Characteristics and biochemistry of chyle (Soto-Martinez & Massie 2009)

Component / Feature	Biochemistry
pH	7.4 – 7.8
Colour	Milky – clear in starvation
Sterile	Yes
Bacteriostatic	Yes
Total Fat	0.4 – 6 g/dl
Cholesterol	65 – 220 mg/dl
Triglycerides	≥1.1 mmol/L (≥ 110mg/dl)
Total Protein	2 – 6 g/dl
Albumin	1.2 – 4.1 g/dl
Globulin	1.2 – 3.1 g/dl
Electrolytes	Similar to plasma
Glucose	2.7 – 11 mmol/L
Chylomicrons	Yes
Cellularity:	
Absolute cell count	≥1000 cell/μL
Lymphocytes	≥80%
Erythrocytes	50 – 600 /mm^3

Buttiker *et al.* (1999) analysed the pleural fluid of thirty-nine children who developed a chylothorax. The triglyceride levels of the children ranged from 0.56 – 26.6 mmol/L, with a median of 4.4 mmol/L. Five of six children with triglyceride levels ≤1.1 mmol/L, had levels ≥1.1mmol/L following a small amount of fat containing milk feed. The sixth child was never fed a milk containing fat. The subsequent and continuing impact of the work by Buttiker

and colleagues is probably due to their inclusion of data from ten children who did not have a chylothorax. In these children, triglyceride concentrations ranged from 0.18 – 0.71 mmol/L with a median of 0.38 mmol/L. This confirmed that chylothorax diagnosis could be made with reasonable confidence if pleural fluid contained triglyceride levels of ≥1.1mmol/L. Concentrations between 0.56 – 1.0 mmol/L were determined equivocal, hence verifying Staat *et al's* (1980) study. These results are further ratified by Beghetti *et al.* (2000) who, following a review of their hospital database for paediatric patients with chylothorax, reported confirmation criteria as pleural fluid analysis, with triglyceride levels of ≥1.0 mmol/l, a milky appearance and a positive Sudan 111 test result.

Other characteristics generally found to be useful in the diagnosis of chylothorax, although inconsistently used across studies, are the total cell count ≥1000 cell/μL, with a lymphocyte count ≥80% (Buttiker *et al.* 1999;Soto-Martinez & Massie 2009). Buttiker *et al.* (1999) however report that 85% of their thirty-nine children with a confirmed chylothorax demonstrated a lymphocyte count ≥90%, implying that the 80% criteria should be raised, although Beghetti *et al.* (2000) felt a reduced lymphocyte count of ≥70% was conclusive. This discrepancy may relate to the small sample size of these studies with both centres recruiting <50 children and demonstrates the need for more clinical research in this area to substantiate findings.

Establishing clear criteria for diagnosing these children will aid in determining the true incidence of chylothorax in this patient group, allow for cross-study comparison and is vital to ensure appropriate, timely and cost-effective treatment and recovery. There appears to be general agreement across the literature on the relevance of biochemical diagnostic criteria, although certain parameters vary, with some clinicians erring on the use of more cautious levels. What remains unclear, possibly due to a lack of detail in the studies and a lack of evidence focusing on the risks and benefits of the diagnostic tests and the small sample size of the studies, is whether all centres currently could and do use all diagnostic tests to confirm a diagnosis, which tests are sufficient to diagnose a chylothorax and whether local guidance or preferences

are applied, and if so, which guidelines are used together with the rationale behind this.

2.6 Risk factors and variables linked to chylothorax development

There are eleven papers, seven cohort studies and four case-series studies, reporting on potential risk factors, perceived causes or aetiology and associated condition or variables of chylothorax development in children (Table 2-7). These studies discuss singly or in combination, three categories of infants and children who developed a chylothorax:

i. Those associated with cardiothoracic surgery.
ii. Those associated with a congenital / neonatal abnormality.
iii. Other co-morbidities.

The evidence will be reviewed under these three categories.

2.6.1 Cardiothoracic surgery

There are three cohort studies that purport to focus on cardiac surgery as a risk factor for the development of a chylothorax (Chan *et al.* 2005, Sandra *et al.* 2011, Mery *et al.* 2013) and one case-series Biewer *et al* (2010). The research design of the latter study negates accurate reporting of risk factors, appearing to report on common variables in those children who developed a chylothorax following cardiac surgery.

Chan *et al* (2005) and Sandra *et al* (2011) imply there is a link between cardiothoracic surgery and the development of a chylothorax, although each study only explores chylothorax development in children in this cardiac surgical cohort, and therefore by definition there is a direct relationship. Furthermore, the accuracy of the risk factors reported in these studies is

questionable due to the small sample numbers and difficulty in accurately analysing and drawing conclusions from such limited data.

Mery *et al's* (2013) and Sandra *et al's* (2011) studies were only accessible from conference abstracts hence the detail of their research is unknown. Mery *et al.* (2013) reports a higher incidence of chylothorax occurring with increased cardiac procedural complexity and in neonates. When comparing the remaining three studies, Chan *et al's* (2005) study appears the most robust. This includes children who had cardiac surgery and did not develop a chylothorax as a comparison group for analysis, although no reference was made to a power calculation. To determine higher 'risk' factors within their sample, characteristics of those children both with and without a chylothorax are compared using chi-squared logistical regression and Kruskal-Wallis analysis of variance testing. They report no statistical differences between the two groups regarding risk factors of sex, weight, body surface area, or the outcome of death before hospital discharge. Post-operative length of stay was noted to be considerably longer in those developing a chylothorax (median of 22 vs. 8 days), confirming the potential impact of this condition. When reviewing potential risk factors they report an increased chylothorax risk between those children that had surgery for heart transplantation, a Fontan procedure, or a Tetralogy of Fallot (TOF) repair.

These four studies described a range of cardiac surgical procedures undertaken in children who subsequently developed a chylothorax. All studies, except Biewer *et al.* (2010), reported a greater risk of developing this co-morbidity following a TOF repair, or a Total Cavo-Pulmonary Connection (TCPC) / Fontan procedure. However, despite reporting these risk factors, only Chan *et al* (2005) and Mery *et al's* study design and analysis support their conclusions, with Biewer *et al (*2010) and Sandra *et al.(* 2011) primarily describing the clinical presentation and diet efficacy in children who developed a chylothorax following cardiothoracic surgery. Other studies (Bond *et al.* 1993;Doerr *et al.* 2005;Milonakis *et al.* 2009;Nguyen *et al.* 1995) report on possible risk factors linked to chylothorax development following cardiac surgery, however the research design of each study focuses on describing the

management strategies prescribed and administered to treat these children, not on establishing risk factors. Hence the conclusions reported in these papers do not appear to be supported by the data and must be treated with caution.

Bond *et al's* (1993) single centre case-series review of twenty-six infants and children who developed a chylothorax following a cardiothoracic procedure reported a patent ductus arteriosus (PDA) ligation as the most common procedure. Whilst this is not a high risk link made by other studies, Nguyen *et al's* (1995) cohort study did identify it as the second most common procedure after complex cardiac surgery including a Fontan and Norwood procedures, with 25% (n=6) developing a chylothorax following a PDA ligation. Both studies were undertaken in the 1980s and early 1990s when a PDA ligation procedure was performed via a thoracotomy, hence involving manipulation close to the thoracic duct. Since this time cardiac surgical techniques have significantly progressed with this procedure now being undertaken via an interventional cardiological approach rather than a surgical procedure, and therefore these findings are now less likely to be relevant.

Milonakis *et al's* (2009) study solely reports on the characteristics of eighteen children who developed a chylothorax following cardiac surgery. The majority of these children developed the chylothorax following a TOF repair n=10 (55%), with a Fontan procedure, n=3 (17%), being the second most frequent reported link. Although Doerr *et al's* (2005) study states it focuses on characterising the aetiology of chylothorax in 203 patients, it is a single centre case-series report reviewing the chylothorax cases occurring in children and adults between 1980 – 2000. The median age of the sample was 54.5yrs and data provided is not age specific. Although they report on cardiothoracic surgery being a cause of chylothorax, this is a descriptive case-series report that does not allow these conclusions to be drawn.

Further ability to compare the above cohort or case-series studies was limited due to small sample numbers and differing sub-group analysis.

Table 2-7 Evidence table showing potential 'risk factors' associated with developing a chylothorax

KEY: ASD = atrial septal defect, AV = atrioventricular, AVSD = atrioventricular septal defect, CoA = coarctation of the aorta, PAIVS = pulmonary atresia with intact ventricular septum, PAVSD = pulmonary atresia with ventricular septal defect, PDA = patent ductus arteriosus, PS = pulmonary stenosis, RVOT = right ventricular outflow tract, TAPVD = total anomalous pulmonary venous drainage, TGA = Transposition of the great arteries, TOF = Tetralogy of Fallot, TCPC = Total cavopulmonary connection / Fontan, VSD = ventricular septal defect

Reference	Research design	Research question	Method	Sample (confirmed chylothorax cases)	Research review / quality
(Beghetti *et al.* 2000). Geneva, Switzerland	• Small Scale Retrospective Cohort Study • Single Centre	To determine the incidence and aetiology of chylothorax in children and to assess therapeutic management approaches	• Database identified, then case note review • Study period 1985 – 1996	• n=51 • Age range 0-16yrs (median 1.65 yrs) • 76% (n=39) of children developed a chylothorax following congenital cardiac surgery • 14% (n=7) post thoracic procedures e.g. oesophageal atresia, diaphragmatic hernia or neuroblastoma • 6% (n=3) were congenital chylothorax • 2% (n=1) following chest trauma • 2% (n=1) spontaneous	• Country – Switzerland • Appropriate research design. Unclear how database identified chylothorax. • Small sample size – includes children ≤16 yrs. 11 yr data collection period • Funding for study: not reported • Source of data – Child's health record – Unclear what data collection tool was or who collected the data. • Data provided – appeared robust • Study reports on aetiology, characteristics of chylothorax in children & treatment • No independent comparison group • Comparative analysis within the study sample, between 3 groups: a) direct injury to thoracic duct, b) thrombosis & or high venous

Reference	Research design	Research question	Method	Sample (confirmed chylothorax cases)	Research review / quality
				• Three etiological groups identified: 1. Direct injury to the thoracic duct (33/51 = 65%) 2. Thrombosis and/or high venous pressure in SVC (14/51 = 27%) 3. Congenital (4/51 = 8%)	pressure, c) congenital – small number. No power calculation reported. • Limited single centre evidence to draw substantive conclusions on associated conditions / risk factors.
(Epaud *et al.* 2008). Paris, France	• Retrospective, Single Centre • Case-series review	To present institutional experience of idiopathic chylothorax in children and to propose therapeutic strategies	• Chart review • Study period 1989-2004	• n=6 • Age range 2-14 yrs (median 7 yrs) • Idiopathic chylothorax	• Country – France – Single centre • Appropriate research design. Unclear how a child was identified as having a chylothorax. ? more children missed. • Very small sample size – no infants. No PMH was given on any of the children. 5 yr data collection period • Focused only on idiopathic chylothorax i.e. not neonatal or following surgery, exact definition unclear. • Funding for study: not reported • Source of data – Child's health record – Unclear what data collection tool was or who collected the data. • Data provided – appeared robust

Reference	Research design	Research question	Method	Sample (confirmed chylothorax cases)	Research review / quality
					• Study did not provide sufficient clinical background on the children, or evidence, to draw any conclusion on associated conditions / risk factors. • No comparison group.
(Chan *et al.* 2005). Toronto, Canada	• Small Scale Retrospective Cohort Study • Single Centre	To determine the incidence, risk factors and outcomes for chylothorax in children following cardiothoracic surgery	• Database identified, then case note review • Study period 2000 – 2002	• n=48 • Age range birth – 20 years (median 5.8 mths) Primary diagnosis: • 25% (n=12) TOF / DORV • 21% (n=10) Hypoplastic left heart • 14.5% (n=7) AVSD • 14.5% (n=7) Complex lesions • 12.5% (n=6) VSD • 6.25% (n=3) TGA • 6.25% (n=3) Simple lesions Higher chylothorax link with those having heart transplantation, Fontan procedure & Tetralogy of Fallot surgery i.e. Increased trauma to the	• Country – Canada • Appropriate research design. Unclear on robustness of how database identified chylothorax. • Small sample size – included young adults ≤20yrs. Median ≤6 mths. 2 yr data collection period. • Funding for study: not reported • Source of data – Child's health record – Unclear what data collection tool was or who collected the data. • Data provided – robust • Study information addresses the research questions. • Comparison group – all cardiac surgical cases during the same time period. No statistical differences noted between 2 groups re: demographics of the children. • Some comparative analysis but no power calculation reported, therefore validity of comparisons

Reference	Research design	Research question	Method	Sample (confirmed chylothorax cases)	Research review / quality
				chest cavity & high SVC pressure.	unclear. • Limited single centre evidence & poor robustness to research design. Links to risk factors possible, but caution needed.
(Doerr *et al.* 2005). Rochester, Minnesota, USA	• Retrospective, Single Centre • Case-series review	To characterise the aetiology of chylothorax patients in one centre and compare findings with those form previous studies	• Database identified, then case note review. • Study period 1980 – 2000	• n=203 (children & adults) • Age range 21 wks gestation – 93 yrs. (median 54.5 yrs) • 50% (n=101) cases due to surgery or trauma. (13.8% (n=28) for CHD) • 44% (n=89) linked to various medical conditions. (16.7% (n=34) malignancies) • 6% (n=13) unknown cause	• Country – Canada – Single centre • Appropriate research design. Clear guidance on how database identified chylothorax. • Large sample size, but mainly adult patients. Unable to confidentially apply results to children. 20 yr data collection period. • Funding for study: not reported • Source of data – Child's health record – Unclear what data collection tool was or who collected the data. • Data lacked depth & difficult to identify specifics of younger patients. • Study information addresses the research questions. • No comparison group. • Unable to draw any conclusions to risk factors in children
(Rocha *et al.* 2006). Northern	• Retrospective Cohort Study • Multi-centre	To accurately determine the causes &	• Case note review • Study	• n=62 • Age range 25-40 wks (median 33 wks). 76%	• Country – Portugal – Multi centre – 6 centres. • Appropriate research design. Data

Reference	Research design	Research question	Method	Sample (confirmed chylothorax cases)	Research review / quality
Portugal	- 6 centres.	prognostic significance of pleural effusions in a population of high-risk neonates	period 1997-2004	(47) were preterm. • Congenital chylothorax – 15% (n=9) • Link to neonates with hydrops fetalis and staphylococcal pneumonia.	collected by notes review – Accurate identification of chylothorax dependent on accurate documentation. • Small sample size. All neonates or pre-term infants. 7 yr data collection period • Funding for study: not reported • Source of data – Child's health record – Unclear what data collection tool was or who collected the data in each centre. How robust was the process? • Data provided identified multiple diagnostic categories. Unclear how infants were categorised in to one over another. • Unknown if authors were able to, or could addressed the research question of determining the 'cause' of pleural effusions, as too many variables. • No comparison group. • Unable to draw any robust conclusions to identifying risk factors in infants who developed chylothorax. But links noted i.e. infants underlying condition.

Reference	Research design	Research question	Method	Sample (confirmed chylothorax cases)	Research review / quality
(Milonakis *et al.* 2009). Athens, Greece	• Small Scale Retrospective Cohort Study • Single Centre	To explore the aetiology and present the institutes experience with the management of chylothorax following congenital heart disease	• Case note review • Study period 1997 – 2006	• n=18 • Age range 5mths–5.6yrs (median 19–20mths) • 55% had a TOF repair • 17% had a Fontan (TCPC) procedure • 5.5% had a VSD repair • 5.5% had an ASD + PS repair • 5.5% CoA repair • 5.5% Aortopulmonary shunt construction • 5.5% PDA ligation Chylothorax noted after median sternotomy in the absence of elevated venous pressure or Fontan circulation	• Country – Greece – Single centre • Appropriate research design. • Data collected by notes review – Accurate identification of chylothorax dependent on accurate documentation. • Small sample size. Infants & children, 9 yr data collection period • Funding for study: not reported • Source of data – Child's health record – Unclear what data collection tool was or who collected the data in each centre. How robust was the process? • No comparison made with those children not developing a chylothorax. • Unable to draw any robust conclusions to identifying risk factors in infants who developed chylothorax. But links noted with cardiac surgical procedures.
(Amoozgar *et al.* 2010). Shiraz, Iran	• Retrospective, Single Centre • Case-series Review	To determine the incidence, risk factors, laboratory findings and outcomes of	• Case note review • Study period 2004–2009	•n=14 •Age range 1 mth – 16yrs (mean 37mths ± 12mths) •64% (n=9) – chylothorax following	• Country – Iran – Single centre • Appropriate research design. • Data collected by notes review – Accurate identification of chylothorax dependent on accurate documentation.

Reference	Research design	Research question	Method	Sample (confirmed chylothorax cases)	Research review / quality
		chylothorax in children		cardiac surgery. (n=6 – BT shunt, n=1 endocardial cushion repair, n=1 Fontans procedure) •Remaining 5 children, 7% (n=1) – congenital chylothorax, lymphangiectasis, Down syndrome, chest tube insertion for pneumothorax, following tracheoesophageal fistula repair.	• Small sample size. Infants & children, 5 yr data collection period • Funding for study: not reported • Source of data – Child's health record – Unclear what data collection tool was used, although data collected was specified. Not identified who collected the data in each centre. How robust was the process? • No comparison made with those children who did not developing a chylothorax. • Limited single centre evidence & robustness to research design unknown. Links to risk factors possible, but caution needed.
(Caserio *et al*. 2010). Madrid, Spain	• Small Scale Retrospective Cohort Study • Single Centre	To analyse the pre and post natal features of congenital chylothorax and the outcomes including mid-term follow-up	• Database identified, then case note review. • Study period 1990 – 2006	•n=29 •Age range 20-36 wks (mean 30 wks) •94% (n=27) diagnosed prenatally •Associated conditions: Foetal hydrops (n=18), congenital heart disease (n=4), Down syndrome (n=1), Intrauterine	• Country – Spain – Single centre • Appropriate research design. Unclear on robustness of how database identified chylothorax. • Data collected by notes review – Accurate identification of chylothorax dependent on accurate documentation. • Small sample size. Neonates only. 16 yr data collection period • Funding for study: not reported

Reference	Research design	Research question	Method	Sample (confirmed chylothorax cases)	Research review / quality
				interventions (n=11)	• Source of data – Child's health record – Unclear what data collection tool was used, although data collected was specified. Not identified who collected the data in each centre. How robust was the process? • Research answered the aims of the research. However, vast number of variables identified, with small sample size, meant specific, robust conclusions impossible. Descriptive information informative.
(Biewer *et al.* 2010). Germany	• Small Scale Retrospective Case-series • Single Centre	To analyse the risk factors for chylothorax in infants after congenital heart surgery and the efficacy of median chain triglyceride diet (MCT)	• Database identified, then case note review. • Study period 2000 – 2006	•n = 26 children (of 282 patients) •Age range – unclear •27% had a TGA repair •15.5% had hypoplastic left heart syndrome •15.5% had an AVSD •11.5% had hypoplastic right heart syndrome •7.6% had a truncus arteriosus repair •3.8% has a VSD •3.8% had an ASD •3.8% had DORV	• Country – Germany – Single centre • Appropriate research design. Unclear on robustness of how database identified chylothorax. • Data collected by notes review – Accurate identification of chylothorax dependent on accurate documentation. • Small sample size. Infants only. 6yr data collection period • Funding for study: not reported • Source of data – Child's health record – Unclear what data collection tool was used, although data

Reference	Research design	Research question	Method	Sample (confirmed chylothorax cases)	Research review / quality
				•3.8% had a TOF •3.8% had a CoA •3.8% had an aorto left ventricular shunt This data suggested that elevated central venous pressure was not a major driver for chylothorax	collected was specified. Not identified who collected the data in each centre. How robust was the process? • Poor demographic data provided – focus of study on MCT diet, not on analysing risk factors for chylothorax. Accurate data analysis difficult.
(Sandra *et al.* 2011). London, UK	• Small Scale Retrospective Cohort Study • Single Centre	To review the aetiology, clinical presentation and outcomes of children developing a chylothorax after congenital heart disease surgery (Conference abstract only)	• Database identified, then case note review • Study period 2005 – 2009	•n=49 •Age range 18 days – 9.5 mths(Median 1.92mths) •12% had a TOF repair •10% had a TCPC repair •2.4% had TGA repair Procedure with the highest associated risk of chylothorax was TCPC	• Country – UK – Single centre • Probable appropriate research design. Unclear on robustness of how database identified chylothorax. • Data collected by notes review – Accurate identification of chylothorax dependent on accurate documentation. • Small sample size. Neonates only. 4 yr data collection period • Funding for study: not reported • Source of data – Child's health record – Unclear what data collection tool was used, although data collected was specified. Not identified who collected the data in each centre. How robust was the process? • Full information is not available due

Reference	Research design	Research question	Method	Sample (confirmed chylothorax cases)	Research review / quality
					to a 'conference abstract' being the only source of information. • Some associated conditions identified opposite, but it is unclear which children made up the remaining 75.4% who developed a chylothorax • Limited single centre evidence. No conclusions able to be made. Awaiting full study publication.
(Mery *et al.* 2013). Texas, USA	• Large Retrospective Cohort Study • Multi-centre	To determine the incidence of chylothorax in children after congenital cardiac surgery or heart transplantation and to determine the associated factors and treatment strategies. (Conference abstract only)	• Database identified. • Study period 2004-2011	•n=2205 •Age range <18years •Conditions linked to chylothorax include complex cardiac procedures and young children, primarily neonates.	• Data collected by database review, however it is not stated how the children were identified. How robust the process was is unclear. • Multiple centres included in the study, but the actual number is not -stated. • Large sample size • Full information is not available due to a 'conference abstract' being the only source of information.

2.6.2 Congenital / neonatal abnormalities

Although the development of pleural effusions in neonates appears to be relatively uncommon, congenital chylothorax has been reported in the neonatal population related to specific clinical conditions including hydrops fetalis. In their multi-centre cohort study Rocha *et al.* (2006) discuss 62 neonates with either 'congenital', or 'acquired' pleural effusions. They identified that 'congenital' pleural effusions accounted for 33% (n=20) of cases and 'acquired' pleural effusions accounted for 68% (n=42). Chylothorax was the most common congenital pleural effusion (n=13) accounting for 65% of the neonates, most commonly seen in infants with Down syndrome, polyhydramnios, Noonan syndrome, Turner syndrome and lymphangiectasis. Al-Tawil *et al.* (2000) reported on the combined 13-year experience of two hospitals, one in Australia and one in Saudi Arabia. Their study population was small with a total of nineteen infants, and primarily focused upon the management practices for congenital chylothorax, reporting 37% (n=7) of their infants with chylothorax to have hydrops fetalis. No study currently provides any indication of the percentage of all chylothorax cases that are congenital in origin.

Although both Rocha *et al.* (2006) and Al-Tawil *et al's* (2000) studies are multi-centred they are both case-series and the sample selection processes applied raise concern. Rocha *et al's* (2006) sample relied on a discharge diagnosis of pleural effusion, chylothorax, hydrothorax or fetal hydrops being recorded in the infant health record. However, no reference or discussion is made clarifying the selection process for these retrospective terms, how reliable practitioners were in recording this information, or the processes in place within the participating six hospitals to identify these terms in the infants health records. A neonate, particularly if premature, may remain in hospital for many months with multiple complications, hence errors and omissions in the accuracy of discharge information are possible. Similarly, Al-Tawil *et al's* (2000) study across two countries appears to rely on including an infant in their study if their health record identified a congenital chylothorax diagnosis. No information is however provided on who identified these infants or how the

process was undertaken. Selection bias may therefore have occurred in both these studies and therefore the accuracy of their results is unknown.

Despite these concerns a more recent retrospective, single centre study from Spain (Caserio *et al.* 2010) supports the above findings, reporting on twenty-nine infants who were diagnosed with congenital chylothorax between 1990 – 2006. 94% of these infants (n=27) were diagnosed antenatally and 66.7% (n=18) were complicated by hydrops fetalis. They report on additional co-morbidities of Down syndrome and cardiac defects of TOF and AVSDs. Although a single centre cohort study, their sample selection process is clearer, with the identification of congenital chylothorax cases being via a computer database, hence sample bias should have been reduced.

Other congenital abnormalities of the lymphatic system including pulmonary lymphangiomatosis and lymphangiectasis are also specifically reported as predisposing neonates to the development of a chylothorax (Faul *et al.* 2000;Moerman *et al.* 1993;Soferman *et al.* 2003), however no evidence is provided on the incidence of it occurring in infants with these underlying diagnoses.

From a research perspective there is no doubt the quality of the above evidence on congenital chylothorax development is poor with study sample numbers being small. However, at present this is the only evidence available to clinicians. Further information is therefore required on the primary diagnostic conditions these infants present with and the incidence of chylothorax occurring as a co-morbidity in the neonatal period.

2.6.3 Other co-morbidities

In addition to the above associated conditions, chylothorax development in children has been reported in other less common situations. Individual case reports have been published describing traumatic thoracic duct rupture

following non-accidental injury (Anderst 2007;Geismar *et al.* 1997), blunt trauma (Beghetti *et al.* 2000;Silen & Weber 1995), spinal surgery (Bhat & Lowery 1997;Shapiro *et al.* 2001) and malignancies including lymphomas and neuroblastomas (Beghetti *et al.* 2000;Easa *et al.* 1991;Ikeda *et al.* 1998). Evidence also suggests that children with Henoch Schonlein Purpura (Cogar *et al.* 2005) and tuberculosis (Grobbelaar *et al.* 2008), together with exceptionally rare conditions including Gorham syndrome (Atalabi *et al.* 2008;Tie *et al.* 1994), and Schimmelpenning syndrome (Greene *et al.* 2007) may also have an increased risk of developing chylothorax as a co-morbidities. The extent of these links are however unclear as evidence is based solely on single case studies.

Having reviewed the literature it is clear that no study offers clinicians a definitive answer to the condition(s) specifically linked to chylothorax development in children. Current data suggests the largest numbers of children with chylothorax occur following cardiac surgery, but other co-morbid conditions have been reported. The combined evidence suggests that clinicians could classify these co-morbid links into five categories:

I. Congenital
II. Traumatic (including surgery)
III. High central venous pressure
IV. Malignancy
V. Miscellaneous

(Soto-Martinez & Massie 2009)

However, there is a need for more population studies focusing on the incidence of chylothorax in children in order to provide robust evidence on co-morbidities and associated surgical procedures, and informing further work on aetiology and treatment efficacy.

2.7 Existing strategies for managing and treating chylothorax in infants and children

No strategy for the treatment of chylothorax in children has been subjected to a randomised controlled trial and current knowledge and practices are based on a number of small retrospective cohort studies or case-series reviews (Beghetti *et al.* 2000;Biewer *et al.* 2010;Bond *et al.* 1993;Buttiker *et al.* 1999;Chan *et al.* 2006;Cormack *et al.* 2004;Nguyen *et al.* 1995).

The main management principles appear to proceed in an escalating fashion. Initially, confirmation of the diagnosis is made, usually from pleural fluid analysis which may include drainage of the chylothorax by thoracentesis, or require insertion of an intercostal pleural catheter. Subsequently the management strategies proceed in a stepwise fashion until drainage ceases, commencing with non-operative conservative medical treatment, progressing to surgical intervention depending on the individual child and their condition (Table 2-8).

Table 2-8 Non-operative management and surgical treatment for chylothorax

Non-operative management	Surgical treatment

• Dietary Modification
  • Medium-chain triglyceride (MCT) diet
  • Total parenteral nutrition (TPN)
• Drug therapy
  • Octreotide (OCT)
  • Somatostatin (SST)
• Adjuvant therapy
  • Steroids
  • Antithrombin
  • Immunoglobulin
	• Surgical Interventions
	  • Pleurodesis
	  • Video-assist thoracoscopic surgical (VATS) approach
	  • Pleuroperitoneal shunt
	  • Thoracic duct ligation

2.7.1 Respiratory support and drainage of chylothorax

Due to the respiratory compromise that develops with chylothorax, there is consensus within the literature that the initial management strategy for these children is to support their respiratory status. This is then followed by aspiration or drainage of the pleural fluid (Allen *et al.* 1991;Bond *et al.* 1993;Soto-Martinez & Massie 2009). Supplemental oxygen therapy may be necessary and this could progress to some children requiring intubation and mechanical ventilation (Allen *et al.* 1991;Caserio *et al.* 2010). Drainage of pleural fluid may be via single or repeated thoracentesis, usually undertaken for congenital chylothorax, or the insertion of an intercostal pleural catheter. This is more commonly seen following surgical procedures or trauma, to allow for the continuous drainage of fluid from the pleural space (Allen *et al.* 1991;Biewer *et al.* 2010;Panthongviriyakul & Bines 2008;Soto-Martinez & Massie 2009). The interventional management strategies of intubation and both chest drainage procedures require the child to be closely observed and monitored, and this necessitates care in a high dependency or intensive care environment.

Although there is consensus in the literature on the above initial management strategies, there is no evidence on the effectiveness of these treatments. Only a few studies provide any detail or comment on the number of occasions a thoracentesis may be required, the length of time an intercostal pleural catheter may remain in situ, or any complication that may develop as a result of these interventions. Indeed this information could only be found in five studies and each reported varied information with no consistency (Allen *et al.* 1991;Biewer *et al.* 2010;Caserio *et al.* 2010;Chan *et al.* 2005;Shih *et al.* 2011).

Of the five studies, all had small sample numbers (n=18-48) with those children who required an intercostal pleural catheter for drainage of their chylothorax having it inserted for a median range of 6-15 days (range of 1-314 days). With the small sample numbers in each study, this wide range in the number of days an intercostal pleural catheter was in situ was not unexpected. From the data presented by Caserio *et al* (2010), Biewer *et al* (2010) and Shih *et al* (2011) it is not possible to identify how many, if any, of

the children were outliers with regard to the length of time they required an intercostal pleural drain in situ. Each study presented their data for the total group, rather than for individual children, hence there is a possibility that their analysis may be spurious. Conversely, four of the children (22%) in Allen *et al's* (1991) study were reported as requiring the drain to be inserted for ≥17 days, with six children (14%) reported in Chan *et al's* (2005) study as outliers, requiring a pleural catheter for ≥57 days (range 57-314 days). These cases therefore skewed both these datasets.

The children in Chan *et al's* (2005) study averaged five months of age when their cardiac surgery was undertaken and intercostal pleural catheter inserted, and required complex procedures which are reported as high risk for chylothorax including; Fontan, Norwood Stage 1, heart transplantation, Blalock-Taussig shunt and bi-directional cavopulmonary shunt (Chan *et al.* 2005;Chan *et al.* 2006;Milonakis *et al.* 2009;Nguyen *et al.* 1995). These six infants had an intercostal pleural catheter in situ for an average of 3.7 months and their total length of stay in hospital would considerably exceed this. The mean length of hospital stay children undergoing these complex procedures, without complications or co-morbidity including chylothorax, has been reported as follows:

- Heart Transplantation – 87 days
- Norwood Stage 1 – median 25 days
- Bi-directional Cavopulmonary Shunt – 8 days
- Fontan procedure – 11 days (range 10-21 days)

(Dean *et al.* 2011;Pagowska-Klimek *et al.* 2011), which are all considerably short than 3.7 months.

Any extended hospital stay exposes the children to the added complications of both hospital acquired and condition related co-morbidities, both of which could detrimentally affect their recovery and their physical and psychological well-being. Children were reported as requiring intubation and mechanical ventilation and multiple thoracentesis procedures by Allen *et al* (1991) and Caserio *et al's* (2010), with the reinsertion of intercostal pleural catheters

being reported in 52.3% (n=23) of Chan *et al's* (2005) children, and one child suffering a cardiac arrest as a result of the chylothorax re-accumulating.

Although these studies all had small sample numbers (n=18-48) with some having similar medians, there was a wide range in the number of days an intercostal pleural catheter was in situ, although this was not unexpected with the small sample numbers.

2.7.2 Dietary modification

The aim of dietary management for the treatment of chylothorax in children is to reduce the flow and pressure of chyle through the thoracic duct, therefore allowing it to heal. Hence, once the respiratory status of the infant or child has been stabilized and pleural drainage of the chylothorax addressed, there is consensus within the literature that first-line treatment is conservative management, consisting of a medium-chain triglyceride (MCT) diet or intravenous parenteral nutrition (Biewer *et al.* 2010;Chan & Lechtenberg 2007;Chan *et al.* 2006;Cormack *et al.* 2004).

The volume of chyle produced by the body increases and decreases with the dietary intake of fat. Typically, dietary fats in a normal diet consist mainly of long-chain triglycerides (LCTs), with a smaller amount of short and medium-chair triglycerides. During digestion, LCTs are absorbed into the fatty walls of the intestinal villi and are reassembled into triglycerides. These triglycerides then combine with cholesterol and proteins to form chylomicrons. The chylomicrons then enter the lymphatic system and are transported as chyle via the lymphatic system into the thoracic duct, which then empties into the bloodstream via the left subclavian vein. The chylomicrons then transport the triglycerides to tissues where they are stored or metabolized for energy (Beghetti *et al.* 2000;McGrath *et al.* 2010).

Medium-chain triglycerides (MCT) do not enter the lymphatic system, being absorbed directly into the portal system and taken to the liver for processing and absorption. This process results in less fluid being absorbed into the lymphatic cells and a reduction in the production of chyle. With less chyle circulating through the thoracic duct, there should be less likelihood of leakage of lymphatic fluid into the thoracic cavity were the duct to be damaged, reducing the risk of chylothorax development and allowing for healing of the thoracic duct.

For those children unable to tolerate enteral feed, modified intravenous total parenteral nutrition (TPN), without lipid, is administered. This consists of a fluid containing glucose, amino acids, lipids, vitamins and minerals that meets all of the child's nutritional needs, but does not increase chyle production (Johnson & Sexton 2006).

All studies reported chylothorax resolution in those children treated conservatively. However recognition of their study limitations is minimal. None suggested their cohort study or case-series report not to be a robust methodology reporting a treatment 'success', and none identified the need for a more robust randomised trial of this management strategy to be undertaken. Whilst the cohort studies of Cormack *et al* (2004) and Chan *et al* (2006), and the case-series of Biewer *et al* (2010), did report on the outcomes of children prescribed and administered a MCT diet versus those that were not, demonstrating an improved research design, the authors' critique of their own research methodology lacks objectivity and depth and therefore reported results require cautious interpretation.

There were wide discrepancies regarding the reported outcomes of solely conservative management of a chylothorax in children, with one centre reporting complete recovery in their seven infants (Chan & Lechtenberg 2007). Others reported varying rates of chylothorax resolution, Marts *et al.* (1992) 87.5% (n=14), Cormack *et al.* (2004) 78% (n=14), Buttiker *et al.*, (1999) 74%, (n=29) and Biewer *et al.* (2010) 71% (n=17). One study reported a resolution

of only 39% (n=7) (Allen *et al.* 1991). The range of resolution rates to this management strategy is therefore broad (range 39-100%) and may reflect the heterogeneous patient group. The definition of treatment success is variable and poorly defined although appears to relate to the child not requiring surgical intervention to aid with chylothorax improvement. However, there is inconsistency within the literature regarding the time frame selected for this surgical intervention with a reported range of 3-59 days (Allen *et al.* 1991;Biewer *et al.* 2010;Chan *et al.* 2006;Cormack *et al.* 2004). Although comparison groups are present within these studies, how the authors are able to conclude treatment success when none considers chylothorax improvement could reflect the natural course of the condition, is unclear. Additionally, these studies focus only on those individuals who developed a chylothorax following a surgical procedure, (either a cardiac or diaphragmatic hernia repair), rather than any other condition associated with the development of a chylothorax. Hence generalizability of these results to other patient groups is unclear. Shih *et al.* (2011) did report a 67% (n=6) resolution rate with all four children who had a primary congenital chylothorax, and two of the five children who developed a chylothorax following cardiothoracic surgery were successfully managed conservatively, although again this sample number is small and there was no comparison group.

Despite the above limitations, these management principles have been extrapolated to children who have develop a chylothorax linked with other conditions (Berkenbosch *et al.* 2003;Goens *et al.* 1992;Tie *et al.* 1994). These studies are case reports commenting on one or two children who developed a chylothorax linked to sepsis shock, Noonan or Gorham syndrome. Of note is that all the children required additional treatment with intravenous (IV) octreotide (OCT) or somatostatin (SST), or surgical intervention to manage their chylothorax. Whilst these reports focused on individual cases rather than larger cohort studies, the lack of chylothorax cessation solely with conservative management in children with these conditions requires further investigation.

Although 70-80% of infants and children who develop a chylothorax following cardiac surgery are reported to gain cessation of their chylothorax either

through a low fat / MCT diet and/or IV TPN (Allen *et al.* 1991;Beghetti *et al.* 2000;Biewer *et al.* 2010;Bond *et al.* 1993;Cormack *et al.* 2004;Shih *et al.* 2011), these results are uncertain as no comparison group, either to 'no treatment' or to 'alternative therapies' was used as a control. It is therefore impossible to know whether the chylothorax would have improved spontaneously, or indeed if pleural drainage, which is first line treatment, could have led to the cessation.

For those children solely on an MCT or low fat enteral feed Cormack *et al.* (2004) recommend they remain on this formula for four weeks, although there appears to be varied opinion with a range of three to six weeks being recommended (Bond *et al.* 1993;Chan *et al.* 2005;Nguyen *et al.* 1995). Biewer *et al*. (2010) report that ten days of MCT or low fat diet was effective in 71% of their chylothorax infants, although Allen *et al*. (1991) and Chan *et al.* (2006) report only a 40% resolution rate at ten days (range 2-16 days). Additionally, it is unclear within the literature when the time period for this treatment commenced, whether this was the date of diagnosis, intercostal pleural catheter removal, completing IV TPN therapy or discharge from hospital (Le *et al.* 1991;Nguyen *et al.* 1995).

For those solely receiving IV TPN, or receiving IV TPN in combination with an MCT/low fat diet, improvement of the chylothorax appears to occur after approximately two weeks (Beghetti *et al.* 2000;Bond *et al.* 1993;Cormack *et al.* 2004;Nguyen *et al.* 1995). There is general agreement that IV TPN is beneficial in the critically ill child who is fluid restricted, but this requires balancing against the disadvantages of IV TPN which include gut stasis, catheter-related sepsis, possible liver damage and cost. Again there appears to be little consensus within the literature on the length of time IV TPN should be administered for chylothorax treatment. This lack of evidence has led many to create a local clinical guideline that reflects individual department experience in the management of chylothorax in children (Chan *et al.* 2005;Cormack *et al.* 2004;Panthongviriyakul & Bines 2008;Soto-Martinez & Massie 2009).

This review of the dietary modification for children who developed a chylothorax indicates there are serious uncertainties within the clinical and organisational decision-making regarding the management strategy for this patient group. The costs to the health service and the morbidity to the children are likely to be high, yet to date there has been no useful evidence to address these concerns.

2.7.3 Drug therapy

The majority of published studies reviewing the management strategies for children who develop a chylothorax focus on the drug therapies. There is one systematic review (Roehr *et al.* 2006) and one literature review (Helin *et al.* 2006) and both focus on the same treatment option for these children; the use of the drugs IV SST/OCT.

Roehr *et al.* (2006) reviewed the evidence relating to the use of IV SST/OCT in children from birth to eighteen years, with the aim of assessing the efficacy and safety of both drugs in the treatment of primary and secondary chylothorax. The literature search was performed between December 2003 – August 2005, however the inclusion dates for the studies are not stated. It is however evident that studies published between 2001 and 2005 were included.

Twenty studies were identified in the review of IV OCT, although the entire sample was only twenty-five children. An even smaller number of studies, five in total, were identified in the review of IV SST, with a total sample of ten children. With minimal studies available for inclusion in the review and each study contributing so few children, the review was based primarily on single case reports, with three studies being case-series of between two and four children. The current level of evidence available for treating these children is therefore poor.

Roehr *et al*. (2006) reported that IV OCT was prescribed and administered to treat the development of post-operative, congenital and spontaneous chylothorax. However SST only appeared to be administered for post-operative chylothorax development, although no rationale was evident for this. SST is a polypeptide with inhibitory actions on the release of gastrointestinal and endocrine hormones, including lymph fluid excretion, (Tauber *et al.* 1994). Experimental studies have shown a decreased thoracic lymph flow following its administration (Markham *et al.* 2000). It has been used less in recent years possibly due to the development of IV OCT, a synthetic analogue of SST with a comparatively longer half-life, which can be administered subcutaneously as well as intravenously (Helin *et al.* 2006) and now appears the drug of choice for these children (Helin *et al.* 2006;Roehr *et al*. 2006). However, experience with both drugs remains limited.

At a similar time to Roehr *et al's* (2006) review, Cannizzaro *et al.* (2006) reported a retrospective cohort study over a 5 year period, 2000-2004 reviewing the data of all neonates and children treated with SST following a persistent chylothorax which failed dietary management. Although their entire population is larger than other studies (n=85), only 15% (n=13) received SST treatment; 46% (n=6) of this subgroup recovered, 31% (n=4) required pleurectomy and 23% (n=3) died. The average age of these three infants was 21 days (range 1-302 days); all had a high amount of chylous drainage prior to SST commencing (median 165 mls/kg/day, range 80-278 mls/kg/day) and 61% (n=8) were receiving one or more inotropic drugs for cardiovascular support, indicating they were cardiovascularly unstable and acutely unwell. The sample size for this group is again too small to apply any results to wider population.

Cannizzario *et al*. (2006) identified their retrospective design as a limitation to their study and reported they had commenced a randomised, double blind, placebo, controlled study of SST in 2001. However following recruitment of five children they had stopped the study due to parental refusal to participate. Parents were unwilling to accept the possibility of placebo treatment with a normal saline solution in the context of complicated or desperate clinical

situations. This is a challenge that would need consideration when planning future more robust research studies in this area, but could be overcome by designing comparative studies of known or standard effective treatment options, rather than treatment versus placebo studies.

Despite IV OCT being more commonly administered over the last ten years, the available evidence appears to lack consistency with regard to the dosing regimens and length of treatment time, with no consensus on identifying the optimal route of administration. Delivery via intravenous infusion identifies a median dose of 68μ/kg/day (range 7.2 – 240μ/kg/day), with a median delivery over 7 days (range 3 – 34 days), whilst subcutaneous delivery identifies a median dose of 40μ/kg/day (range 2 – 68μ/kg/day), with a median delivery over 17 days (range 8 – 43 days) (Helin *et al.* 2006;Roehr *et al.* 2006).

Reporting management strategy success based on uncontrolled observational studies will always be prone to bias towards the treatment effect. In these children where length of treatment may be prolonged, there can be confusion between the treatment effect, supporting strategies aimed at symptom relief or mitigation of adverse effects, interventions aimed at cure and the natural history of the condition where closure of the thoracic duct defect could be spontaneous. Whilst the former aim to stop the adverse effects of the disease, an intervention could, if used in isolation, result in worse outcomes because unless they are genuinely effective, they neither cure nor alleviate symptoms.

Evidence regarding the safety and efficacy of both drugs is also limited. The Cochrane Review (Das & Shah 2010) which focuses on the efficacy and safety of IV OCT in the treatment of chylothorax in neonates, does not dispute the promising findings in current studies (Helin *et al.* 2006;Rocha 2007;Roehr *et al.* 2006), but reports inconclusive findings due to methodological bias. Of the studies available for inclusion in this interventional review, none met their eligibility review criteria as all those retrieved were case reports. The poor quality of the available evidence therefore concluded that the safety and

efficacy of IV OCT in the treatment of chylothorax in neonates had not been properly evaluated and practice recommendations could not be made.

Prior to the publication of the Cochrane Review and in the absence of controlled clinical trials using IV SST/OCT, both Roehr *et al.* (2006) and Helin *et al.* (2006) advocated that IV SST/OCT could be considered in the treatment of refractory cases of chylothorax in infants and children, although first-line treatment of an MCT diet, IV TPN, fluid replacement and infection control should initially be undertaken.

The above aspects highlight the challenges of clinical decision-making in the face of poor quality evidence. Evidence-based medicine should be at the forefront of good clinical practice, and where there is a disparity between the available evidence and children who require treatment a sizeable problem exists.

2.7.4 Adjuvant therapy

Additional supportive therapies for these children are referred to within the literature, and link to some of the complications that children who develop a chylothorax may experience, including malnutrition, hyponatraemia, fluid imbalance, respiratory distress, increased risk of thrombosis and secondary immunodeficiency. However none has been extensively reported on nor studied (Bernet-Buettiker *et al.* 2006;Wasmuth-Pietzuch *et al.* 2004). Orange *et al.* (2003) reported on a series of eight infants who received intravenous immunoglobulin (IVIG) to maintain immunoglobulin G (IgG) levels within normal ranges, having developed a chylothorax following cardiac surgery, or diaphragmatic hernia repair. 75% (n=6) of the infants had severe infections prior to the administration of IVIG, compared to 50% (n=4) who developed a severe infection during the period of IVIG administration. Although the authors reported the preservation of some levels of antibodies with the IVIG therapy, they acknowledge that the study was not controlled, they could not

associate any clinical immunodeficiency with chylothorax development and reported that IVIG replacement could not be shown to be clinically beneficial.

Corticosteroid therapy in chronic pleural effusions, particularly following a Fontan procedure and in association with Noonan syndrome has also been reported (Chan *et al.* 2005;Goens *et al.* 1992). The evidence base to this management strategy is poor and there appears to be no clear reason to explain how this may resolve a lymphatic leak, or the drug dose ranges that should be prescribed. Furthermore the rationale appears to contradict the aim of preventing infection highlighted by the IVIG treatment. Steroid therapy is therefore not currently advocated as routine management in these children.

Other reported supportive therapies have included the use of protein supplements to maintain total body protein stores and serum albumin concentration levels (Cormack *et al.* 2004), and intravenous antithrombin supplements to replace losses in chyle following chylothorax development after cardiac surgery requiring cardiopulmonary bypass (Bernet-Buettiker *et al.* 2006).

2.7.5 Surgical intervention

Reference to surgical management of children who developed a chylothorax is evident within the literature and there is acceptance that it should be considered when medical management fails, or there is persistent and/or high volume chyle leak that does not appear to resolve (Beghetti *et al.* 2000;Marts *et al.* 1992;Milonakis *et al.* 2009). The criteria to progress from medical management are not standardised, however it is reported that if, despite conservative treatment lymphatic leakage continues beyond two weeks, or if large fluid and nutritional losses present a danger to the child or possible metabolic complications, operative intervention is indicated (Marts *et al.* 1992;Milonakis *et al.* 2009;Pego-Fernandes *et al.* 2003). The evidence base behind this management strategy is poor, with no published research studies focusing on this specific aspect of care, and minimal agreement within the literature on a consensus of timing for any surgical procedure. Some authors

advocated three to four weeks of medical therapy before surgical intervention (Beghetti *et al.* 2000;Bond *et al.* 1993;Buttiker *et al.* 1999;Nguyen *et al.* 1995), another ten days (Le *et al.* 2010) whilst one suggests the case for early surgery should be made when there is a well identified site of chyle leak and high flow that would preclude spontaneous healing (Soto-Martinez & Massie 2009). Surgery in this latter case was undertaken on day nineteen. This disparity could be explained by the number of children who appear to respond well to conservative, medical management, with only 8-27% requiring subsequent surgical intervention (Bond *et al.* 1993;Chan *et al.* 2005;Liu *et al.* 2005;Nguyen *et al.* 1995;Wolff *et al.* 1999). However, assuming any degree of causality when there is such limited robust evidence would be inaccurate.

Various surgical interventions have been described for chylothorax management including thoracic duct ligation, pleurodesis and pleuroperitoneal shunts (Bond *et al.* 1993;Chan *et al.* 2005;Liu *et al.* 2005;Wolff *et al.* 1999). Preference for a chosen procedure appears to be hospital specific with little consistency across centres, although thoracic duct ligation and pleurodesis are the more common approaches reported (Chan *et al.* 2005;Chan *et al.* 2006;Nath *et al.* 2009;Pego-Fernandes *et al.* 2003). Comparing the success of these differing procedures is problematic due to the diverse underlying conditions of the children and the fact that reporting appears to be based on whether there was chylothorax resolution following any surgical procedure. This implies that the procedures were being undertaken as curative interventions rather than in a supportive capacity to improve symptoms, although this was not made clear in any study.

The literature discusses the varying surgical options available in the management of these children, with an inference that surgical intervention may provide definitive management which could shorten hospitalisation and potentially reduce the risk of malnutrition and immunosuppression, and consequently infection in these children. However, no randomised controlled trial has been conducted to provide robust evidence for optimal management and therefore neither surgical management nor pleural drainage, MCT/low-fat

diet, IV TPN, OCT or SST therapy is proven to be more beneficial. A lack of clarity therefore continues to exist.

2.8 Chapter summary

This review of the literature identifies that children do develop chylothoraces, although the evidence base to support a greater understanding of this condition in this patient group is of poor quality due to limited sample numbers, study design and retrospective data. For the children suffering from this co-morbidity, and their families, the impact can be significant, and the subsequent financial implications on the National Health Service (NHS) are considerable. The assumed infrequency of the condition occurring is emphasised by the lack of robust published research, with authors reporting cases primarily through single centre small scale retrospective cohort studies or single centre case-series (Amoozgar *et al.* 2010;Caserio *et al.* 2010;Doerr *et al.* 2005;Nguyen *et al.* 1995). This potentially adds to the perception of the rarity of the condition.

To an extent, these studies are beneficial in helping to understand the context of chylothorax and may be useful in planning future epidemiological and interventional studies. They do provide some valuable information on the incidence of chylothorax in single centres in differing countries, the primary diagnostic features of these children together with the management strategies prescribed and administered to treat them, all of which are of relevance.

However, whilst chylothorax in children has been reported following cardiac surgery and during the neonatal period, the true incidence of the condition occurring in the UK paediatric population is unknown. Additionally, there is little information available to identify those children affected by chylothorax, little understanding of which management strategies are most effective, and poor available data identifying how long children remain in hospital, what additional morbidity they experience, or their discharge destination or outcome.

These gaps in knowledge result in limitations in the current clinical practice provided to those children who develop this condition, and in the pre and post-operative information provided to their families. A lack of clarity in understanding which children develop chylothorax and its true incidence in the UK results in this condition either not being specifically discussed with parents of susceptible children, or the possibility of it occurring being amalgamated into a general comment regarding potential complications following cardiothoracic surgery. Neither of these are best practice. Providing families with accurate information regarding possible complications associated with cardiac surgery is vital to ensure informed consent is obtained and families are adequately and appropriately prepared.

Whilst conservative, medical management is the first line treatment for these children, the decision making processes on when to move from one treatment option to another and at what point to escalate to surgical intervention are inconsistent. Whilst these decisions are based on the individual child's condition and possibly local practice guidance, they vary between clinicians, tending to be based on clinicians previous experience and may fluctuate on a daily basis depending on the child's response to the prescribed care. This leaves the parents unclear and confused regarding how their child is being treated, the length of treatment and what the potential outcomes.

Health professionals need to be able to predict those children at risk, optimise the care for these children and their families, improve their outcome and assist in influencing and planning a future children's research agenda. There needs to be increased national and international understanding of the scale of the problem, identification of the potential risk factors associated with the condition and recognition of children most susceptible to developing a chylothorax, in addition to studies undertaken to robustly evaluate current treatment options, their effect, and outcome. Multi-centre, national and international research studies addressing these knowledge gaps need to be undertaken.

The following chapter identifies the research questions generated as a result of the dearth of clinical information available on children who develop a chylothorax. They are aimed at describing the current incidence and patient profile for this population within the United Kingdom (UK), with the additional intention of describing the management strategies used to treat the children and to establish information regarding their discharge destination or outcome. The chapter also identifies the methodological approaches employed to address these questions and describes the study design used to generate the data. Literature is reviewed in relation to the research method selected.

3. Study Design and Methodology

3.1 Introduction

As outlined in the previous chapter, critical analysis of the literature relating to chylothorax in children identified a dearth of robust evidence. This paucity could detrimentally impact on the quality of care provided to these children and their families and influence the efficiency of those healthcare institutes providing their care.

Current available information on chylothorax in children identifies an incidence of 3.2% (3,200 in 100,000) following cardiac surgery, with a small number of cohort and case controlled studies reporting on apparent risk factors linked to chylothorax development and existing treatment strategies administered to manage these children.

However, as discussed in Section 2.8, the current gaps in the literature centre around the need to identify the true incidence of chylothorax occurring in children, clarify which children are affected by the condition, understand which treatment strategies are most effective, identify how long the children remain in hospital and establish their discharge destination or outcome.

3.2 Research Aim and Questions

3.2.1 Research aims

The primary aim of this study was therefore to establish the current incidence and describe the patient profile of children who developed a chylothorax in the United Kingdom (UK).

Secondary aims were to identify and describe the clinical management strategies prescribed and administered to treat these children, together with

establishing information regarding the children's discharge destination or outcome.

3.2.2 Research questions

Study questions formulated to address these aims included:

- What is the current incidence of chylothorax development in children in the UK?
- What are the demographic and clinical features of these children?
- How do clinicians diagnose a chylothorax in children?
- What management strategies are used to treat these children?
- How long do these children remain in hospital?
- What is the discharge destination or outcome for these children?

3.3 Research Design

3.3.1 Introduction

Having reviewed the literature on chylothorax in children, clarified the gaps in current knowledge and decided on the research questions, a quantitative research design to this study was identified as the most appropriate.

The study was non-experimental and primarily necessitated a prospective, observational descriptive design that would provide current incidence data as well as detailed clinical information on children who developed a chylothorax in the UK. Clinical information relating to the children's demographic characteristics, the methods used to diagnose the chylothorax, any co-morbidities experienced by the children, the treatment strategies employed and the children's discharge destination or outcome were required. Depending on the number of children and their location, multiple clinicians in multiple hospitals needed to be contacted. Consideration was given to the differing research designs within epidemiological studies including cohort, case

controlled, cross-sectional (prevalence) and ecological studies (Grimes & Schulz 2002;Mann 2003), however only the latter was suitable to address this study's aims and research questions. The necessity for the primary data collection to be prospective rather than retrospective related to the study aims of establishing the true incidence of chylothorax and the clinical features of the condition. Accurately collecting these data retrospectively from differing clinicians in multiple UK hospitals would have been unattainable.

Whilst prospective cohort studies do provide incidence data, this research design is based on following selected group(s) of individuals who do not have the outcome under investigation to see if over time they develop the condition. Within the group(s) those that do not develop the condition are used as an internal comparison control (Mann 2003). This study was attempting to clarify the incidence of chylothorax development in children across the UK, hence selecting and following a cohort of children would not have addressed the aims of the study or the research questions. Furthermore, given the current evidence-base, identifying which cohort to follow would have been problematic and might have limited the findings to a specific clinical group. Case controlled studies which are retrospective and more focused on aetiology, identify a group of individuals with a condition together with a comparison group without the condition, thus determining the importance of a particular variable in relation to the presence or absence of the disease. These studies have been applied to children who develop chylothorax, however their retrospective nature precludes them from calculating incidence or relative risk. Although they can be used to calculate odds ratios (Mann 2003), this particular research design would not have met this study's aims. Furthermore, using either a cohort or case-controlled study design would have been further hampered by the insufficient evidence on incidence, the challenges in accessing multiple hospital sites and the complexity in following children over time as they transfer from one hospital to another during their recovery. Similarly, a cross-sectional (prevalence) study could have been undertaken, although it would not have addressed this study's research aims or questions relating to incidence or knowledge of the child's discharge destination or outcome, as the focus of these studies is to review cases existing 'at that point in time' (Shields & Twycross 2003).

Ecological studies however, examine the rates of a disease or condition within a population as well as describing the individual population members. These were both key aims of this study hence an appropriate research design. The development of chylothorax in children is reportedly a relatively rare condition with small population numbers, hence within this design category a national surveillance study that identified all the children who developed this condition in the UK during a specific time period, would allow calculation of the actual incidence, together with reporting on the features and outcomes of the children. Paediatric surveillance studies have an important public health role in collecting reliable and timely information regarding the distribution and determinants of a condition or disease in the population and subsequently facilitate effective healthcare responses to reduce morbidity and mortality to improve health (Nicoll *et al.* 2000).

3.3.2 Surveillance methodology

To answer this study's research questions, the study design necessitated identifying children across the UK who developed a chylothorax within a defined time period. Following this, access to data on these children was required.

Due to the unknown population size of this study and a lack of clarity in knowing the exact clinical settings in which these children would be receiving care, achieving complete ascertainment for the study was always going to be challenging. Optimising ascertainment by linking the study into an existing, robust surveillance, data collection systems would assist this process.

The British Paediatric Surveillance Unit (BPSU), hosted by the Royal College of Paediatrics and Child Health (RCPCH), London and supported by the University College London (UCL) Institute of Child Health and the Health Protection Agency (HPA), is one such surveillance system which supports research aiming to help improve standards of medical care and education and provide

information to the public on the health care of children (BPSU. 2012). Via the RCPCH, the BPSU has access to over 3,400 members, with the vast majority being paediatricians or child health professionals based in the UK, all of whom are encouraged to participate in the research studies supported by this organization.

The BPSU scheme supports health professionals in undertaking approximately twelve research surveillance studies a year, which are required to fulfil the following criteria:

- the condition of interest must be a rare childhood infection or disorder (or a rare complication of a more common disease)
- have low incidence (less than 300 cases a year) and requires ascertainment of cases on a national scale in order to generate sufficient numbers for study
- addresses the epidemiology of a condition and/or variations in practice
- is of scientific or public health importance
- has achievable aims
- are appropriately resourced and managed
- use additional alternative data sources (not mandatory)
- following BPSU adoption, the study receives MREC and NIGB approval and conforms to Caldicott and Data Protection procedures. (BPSU 2011).

The process for submitting an application to the BPSU consists of two peer review phases. Initially a screen phase where submission of an initial application to the BPSU Scientific Committee based on an outline of the study, demonstrating adherence to the eligibility criteria is submitted. Once approved, phase two involves submission of the full application with the research questionnaire and public information leaflet to the Scientific Committee (Appendix 3 and Appendix 4). Whilst some aspects of the study design including the general eligibility criteria, reporting processes, minimum length of time for the study, use of a questionnaire based data collection tool, the questionnaire length and generic data requests e.g. age and ethnicity, are prescribed by the BPSU, remaining aspects, including the questionnaire design,

inclusion and exclusion criteria, data collection process, access to additional data sources, data entry and analysis, are determined by the researcher.

The data collection, or reporting system within the BPSU is an 'active' but voluntary process whereby on a monthly basis the BPSU office sends out cards to the entire network of paediatricians of all specialities registered with the RCPCH requesting for cases of conditions under surveillance to be reported to the unit on the BPSU 'orange card'. The 'orange card' contains a list of conditions under surveillance and a request to report any, and all new cases, or 'none seen'. At this stage no detail regarding the clinical case is reported or requested Follow-up reminders for completion of each monthly orange card are sent out after two months (BPSU. 2010). Participants are expected to return the cards regardless of whether they have cared for or seen a child with one of the surveillance conditions. This is an important feature of the scheme, which allows the BPSU to measure compliance to the reporting system (Knowles *et al.* 2006) (Appendix 3).

On receiving a positive case report, albeit on clinician judgement, the BPSU informs the relevant study investigator or team and they send out a questionnaire to the reporting clinician in order to gather data relating to the clinical condition under investigation (Figure 3-1). Only once the questionnaire has been completed and returned can the study investigator or team make an informed decision on confirmation or not of the case.

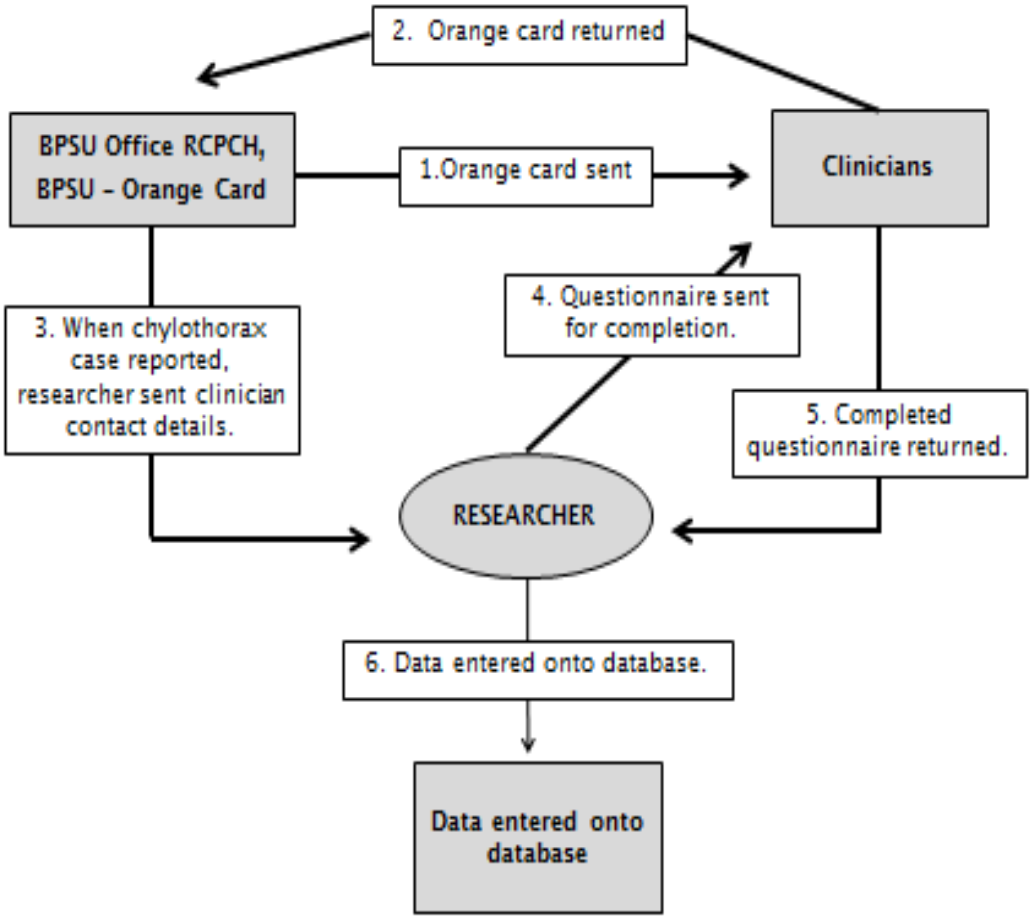

Figure 3-1 Flow diagram showing data collection process

3.3.3 Data ascertainment

One of the challenges of surveillance studies has been the quality of the data collected and the completeness of ascertainment of those affected (Nanan & White 1997). Despite some diseases or conditions having a high incidence or prevalence, numbers can be underestimated due to under-reporting. Explanations for this have included:

- Poorly defined criteria for diagnosis.
- Missed diagnosis.
- Poorly designed surveillance systems.
- Lack of awareness of the need to report cases (Nanan & White 1997).

With the poor reporting of cases potentially resulting in incidence being underestimated, the relevance of ensuring completeness of data ascertainment to this study was highly applicable, hence careful consideration was given to each of the above points. Definition of the criteria for chylothorax diagnosis and therefore the inclusion criteria for the study were mapped to previously reported diagnostic parameters (Section 2.5) and included both laboratory confirmation of lymphatic fluid and subjective clinical decision making criteria (Section 3.5.6.1.). The aim being to encourage clinicians to report all children with a confirmed, or suspected chylothorax to the study investigator, who could then review and confirm each case as necessary. Additionally, prior to the study commencing, these criteria were promoted to all clinicians registered with the BPSU and were further circulated in the covering letter that accompanied the questionnaire. By considering these aspects as well as linking the study to an established UK surveillance system, data ascertainment would be optimised and the reasons identified for under-reporting by Nanan & White (1997) would be addressed.

Furthermore, in addition to the above challenges were the added concerns that study case numbers were likely to be small, there was the potential for variation in how chylothorax was coded and the likelihood of primary diagnoses taking precedence over the recollection or reporting of co-morbidities such a chylothorax. Each of these concerns denoted that the chylothorax diagnosis could be overlooked and therefore all aspects required considerable forethought.

To ensure enough information was obtained to answer the research questions, the study required a data collection instrument that specifically defined the case criteria and variables. The instrument needed to provide enough depth of data that allowed for analysis, interpretation and results that would inform practice. Furthermore, as a disease surveillance study it was essential to be able to maximize the ascertainment of true cases and remove incorrect or duplicate cases, in order to obtain an accurate estimate of incidence and to avoid ascertainment bias (Knowles *et al.* 2006). This would allow for the true

incidence of chylothorax in children within the UK to be identified, as well as increasing the understanding of the treatment strategies used to manage these children and identify their discharge destination or outcome.

Ascertainment bias can occur when inaccurate or incomplete results are produced from a non-typical sample and conclusions then made about the entire population (Tilling 2001). In any data collection attempting to minimise bias prior to the start of a study is essential. Using a single data source to estimate an incidence within a population makes an assumption that no case would be missing from that source (Tilling 2001). Whilst this assumption could be accurate, increasing the number of reporting sources, particularly within surveillance studies is encouraged (Knowles *et al.* 2006;McCarty *et al.* 1993) and would assist in identifying cases not captured from a single source, thus allowing for the confirmation of true cases and greater acceptance of the estimation of completeness of ascertainment (Knowles *et al.* 2006).

The literature which focused on children who developed a chylothorax in the UK, identified they were cared for in neonatal and paediatric settings in tertiary, tertiary specialist and district general hospitals (DGH). The framework for hospital-based paediatric care in the UK where tertiary and tertiary specialist hospitals work in close collaboration with their regional DGHs, would support this finding. Therefore, in order to optimise case ascertainment and collect information on all children who met the inclusion criteria for the study, there was a need to identify and access data sources that would report on the number of cases under investigation, irrespective of the child's primary diagnosis or location of care. Four differing data sources were therefore identified;

- The British Paediatric Surveillance Unit (BPSU) reporting system.
- Congenital Cardiac Audit Database (CCAD).
- Hospital Episode Statistics (HES) data.
- Paediatric Intensive Care Audit Network (PICANet) database.

Accessing four differing data sources that overlapped in their population reporting systems would minimise ascertainment bias and would facilitate the

use of a capture-recapture analysis method to assess both the quality and completeness of the data (Hook & Regal 1995;McCarty *et al.* 1993;Nanan & White 1997). A method identified as of particularly value for use in surveillance studies (McCarty *et al.* 1993;Nanan & White 1997).

3.3.4 Capture-recapture

Capture-recapture techniques have been used over the years in demographic, epidemiological and disease surveillance studies (Morrison & Stone 2000;Wittes *et al.* 1974) to estimate the number of additional cases that could have been missed by all reporting sources, hence identifying the 'true' number of cases 'N' in the population (Figure 3-2) (Knowles *et al.* 2006). Statistical formulae allow estimation of this 'true' population number (Hook & Regal 1995) (Appendix 5).

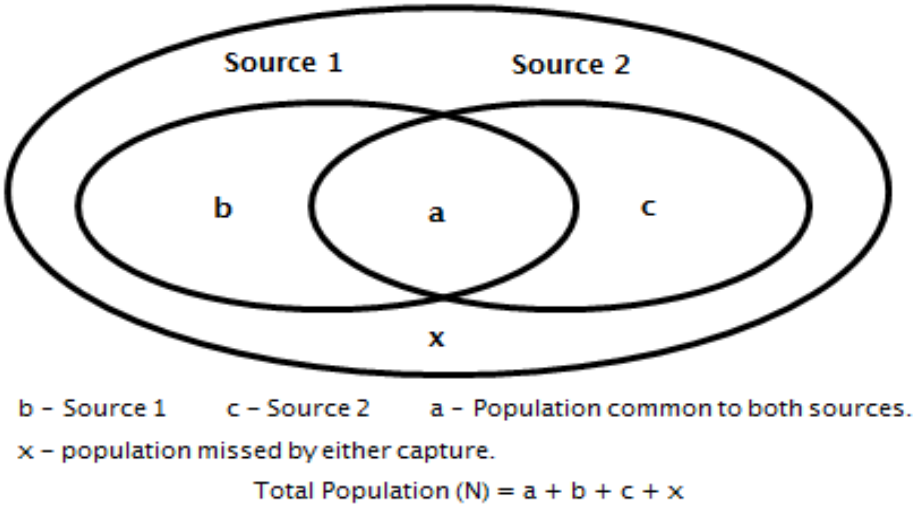

Figure 3-2 Two source capture-recapture method (Knowles *et al.* 2006)

The application of this technique is however reliant on the presence of four assumptions:

1. Closure – The population under study must be 'closed', so that there is be no migration or loss of cases from the population during the study period.

2. Independence – The sources must be independent of one another, i.e. the probability of appearing in one group is not affected by the probability of being in another.

3. Homogeneity – Each case in the defined population has an equal probability of being 'captured' in any sample.

4. Perfect Match – cases identified in one source can be perfectly matched to another source without error i.e. no mismatches or non-matches.

(Knowles *et al.* 2006;McCarty *et al.* 1993;Nanan & White 1997).

Application of each of these four assumptions to the four differing data sources in this study was necessary to ensure there was the same probability of each case being identified in each data source.

All four data sources should have met the criteria for 'closure'. The inclusion criteria for the study were specific and well defined (Section 3.5.6.1) and although there may have been migration in the location of the child's care either within or between hospitals, there should have been no loss of cases from the population during the study period.

Each data source was assumed to be 'independent' of the others and identification in one dataset should not have affected the probability of a case being identified in another. This assumption was however difficult to verify, and has been acknowledged as challenging to achieve in health care settings (Hook & Regal 1995). For example if cases of chylothorax had been more likely to be identified in HES or CCAD data as a result of them being identified through the BPSU surveillance system, then sources would demonstrate a 'positive dependence' (Hook & Regal 1995). This could lead to the completeness of ascertainment being overestimated, and the entire population underestimated. Conversely, if cases of chylothorax were less likely to be

identified by HES or CCAD data, once identified by the BPSU system, then a 'negative dependence' would occur and an overestimation of the entire population was possible (Hook & Regal 1995).

Achieving case 'homogeneity' between the data sources, however, proved impossible and case identification bias existed. The availability of data from the four data sources varied both within the country and clinical speciality from which they collected data on children who developed a chylothorax (Table 3-1). Table 3-1 identifies the BPSU collected data on children from all the study countries, HES collected data on all children who developed a chylothorax but only from England, CCAD and PICANet collected data from all the study countries, but the former only collected information from those children with an underlying cardiac focus to their condition and PICANet only collected data on children who had been admitted to a paediatric intensive care unit.

Table 3-1 Inclusion population for each of the four UK data sources

	BPSU	HES	CCAD	PICANet
England	√	√	√	√
Wales	√	X	√	√
Scotland	√	X	√	√
Northern Ireland	√	X	√	√
All chylothorax cases	√	√	X	√
Chylothorax cases (cardiac linked only)	√	X	√	X
Chylothorax cases (linked to a paediatric intensive care admission)	√	X	X	√

The aim had been to achieve a perfect match between 'paired cases' across the data sources by cross-referencing each case via their unique patient identifier(s), thus ensuring any duplicate case would not be included in the entire population. This aspect also proved challenging as the patient identifiers received from CCAD and PICANet were limited and therefore the ability to cross-references cases was restricted.

Attempting to ensure an ascertainment-correct population for this study was therefore not without its difficulties. The study would clearly not meet all the expectations for applying a capture-recapture analysis technique across the four data sources, and therefore although identified as a method of particular value for use in surveillance studies (McCarty *et al.* 1993;Nanan & White 1997), this approach could not be successfully applied to this study. However a differing approach focusing on the cross-validation of the data from one key source (BPSU) to the other three data sources (CCAD, HES and PICANet), in the form of data triangulation could be applied (Halcomb & Andrew 2005).

A sub-group analysis of the data would however allow facilitation of a capture-recapture technique. Once the BPSU data had been analysed and cases reported by centres in England extracted, all four assumptions could be met by this data source and the HES data. The resulting sub-group would enable a perfect match to be made between all 'paired cases' via their unique patient identifiers.

3.3.5 Triangulation

The concept of triangulation in research focuses on the use of two or more research methods to strengthen the overall study design and the researchers' ability to interpret the findings (Begley 1996;Halcomb & Andrew 2005). The concept has been used more commonly in the field of navigation where triangulation describes the process of using two known points to determine the location of a third (Breitmayer *et al.* 1993;Shih 1998). It was, and has subsequently, been viewed within the research field as providing a sense of

confirmation of data through the enhancement of validity and confidence in the findings (Begley 1996;Breitmayer *et al.* 1993;Coyle & Williams 2000;Sandelowski 1995;Shih 1998). This concept is supported by Denzin & Lincoln (Denzin 2005) who recognise that the combination of using multiple methods and perspectives in a single study adds rigour, breadth and depth to an investigation. They state that triangulation is not a tool for validation, but an alternative to it that adds a depth of understanding to the phenomena in question. This suggests a completeness function as well as a confirmatory function within triangulation (Nolan & Behi 1995). A view however some researchers opposed, believing that the initial concept was taken from a technical term used in navigation and as such should be used metaphorically to refer to the use of multiple measure to converge on a single construct and should consequently be reserved solely for 'designating a technique for confirmation', (Sandelowski 1995).

Some researchers however do now appear to accept that no one single research method or theoretical perspective applied in isolation always has the ability to provide in-depth, detailed understanding of humans and their health related needs (Nolan & Behi 1995). Indeed Shih (1998) and Sandelowski (2000) acknowledge the complexity of modern human phenomena necessitates the use of more complex and multiple research designs to fully capture these. The intention within this study was not to combine differing research methodologies or designs, but to utilise the concept of triangulation to access multiple data sources to verify case numbers and optimise case ascertainment and therefore enhance the data collection process. Furthermore, triangulation which is seen to strengthening a study's reliability with a combination of methods or perspectives, has the potential to provide a richness of detail and a more complete understanding of the phenomenon, especially when there are multiple perspectives to consider (Robson 2011;Shih 1998). Therefore, the purpose of a triangulated research design in today's current and more contemporary setting could be seen as providing 'confirmation' and/or 'completeness' to a phenomenon under investigation (Shih 1998;Streubert 1999).

'Confirmation' refers to the process of examining and comparing data gathered from multiple sources, to explore the extent to which findings converge or are confirmed cases (Casey & Murphy 2009). Whilst 'completeness' of data is concerned primarily with gathering multiple perspectives from a variety of sources, to gain a thorough understanding of an area being investigated (Shih 1998).

Denzin & Lincoln (2005) identified four types of triangulation; method triangulation, theory triangulation, data triangulation and investigator triangulation, with Kimchi *et al* (Kimchi.J. *et al.* 1991) adding analysis triangulation more recently, and Begley (1996) identifying a final category of multiple triangulation where more than one type of triangulation is used in analysing the same event.

Data triangulation, which collects information from multiple sources with similar foci was the only category of triangulation relevant to this study. The aim therefore was to use this concept to identify any dissonance between data sources and interpret the findings accordingly. Consideration of data quality and completeness between the data sources would be of particular relevance.

3.4 Conduct

3.4.1 Ethical approval

The NHS Research Ethics Committee (REC) and the National Information Governance Board (NIGB) approval (Section 1.3) permitted access of data from the BPSU and HES datasets, with the NIGB approval additionally sanctioning agreement to access limited data from the CCAD and PICANet datasets.

3.4.2 Consent

As a result of a lack of direct patient involvement, consent issues in epidemiologic and surveillance studies vary from other research methodologies (Coughlin 2006). Within these studies patient consent focuses on informed consent, principally to ensure that research participants make a free choice in their participation (Coughlin 2006). However, informed consent may be waived in circumstances when obtaining consent is impractical, the risks are minimal, and both the risks and potential benefits of the research have been reviewed and considered by the appropriate research ethics and governance committees (Coughlin 2006).

With no direct patient involvement, patient consent was not a requisite for this study, however adherence to strict guidelines, and an application to the National Information Governance Board (NIGB) was required for support under Section 251 of the National Health Service Act 2006 (Health and Social Care Act. 2008). The NIGB was the governing body established to enhance public contribution and involvement in research and to ensure that patient identifiable information needed to support NHS research activity was accessible without the consent of patients, but in a way that fully protected their anonymity. Under the governance of the 2008 Act, the NIGB assesses applications by medical and research institutions to use non-anonymised information about patients without their consent (NIGB. 2010), a requisite therefore required for this study.

Additionally, a letter of support from the local NHS Trust Caldicott Guardian was necessary, together with documented evidence that the study investigator agreed to comply with the principles outlined in the Caldicott Report (Health Protection Agency 1997).

3.4.3 Data confidentiality and anonymity

The study adhered to the UK legislation that addresses confidentiality of personal information including Health and Social Care Act 2008 (Health and

Social Care Act. 2008), Data Protection Act 1998 (Data Protection Act 1998) and the Human Rights Act 1998 (Human Rights Act 1998). All data were managed according to the Systems Level Security Protocol (SLSP) and governed by the host Trust Information Governance Policy.

The physical security system comprised of data entered onto a password protected Trust secure server from the Chief Investigators office. To ensure confidentiality and security of personal information, the electronic data were held in two discrete password protected databases, with the patient identifiable information being separate from the main database.

Particular attention was taken to ensure that patient information collected was the minimum necessary to allow for optimal case ascertainment matching, removal of duplicate cases, contacting notifying clinicians and achieving the research objectives. No patient identifiable information was passed between or within the data sources.

3.5 Study Method

3.5.1 Introduction

In this section a description of the target population will be provided, together with a detailed review of the four data sources. This will be followed by an account of the data management and descriptive and statistical analyses undertaken.

3.5.2 Target population

The target population was any child ≤16 years of age, including neonates ≥24 weeks gestation, who developed a new chylothorax in the UK between 1st June 2010 and 30th June 2011.

3.5.3 Estimated population

Prior to the commencement of this study, the number of children who developed a chylothorax in the UK was unknown. Published data quoted the incidence of chylothorax development following cardiac surgery as 2.5% (Beghetti *et al.* 2000;Buttiker *et al.* 1999), with a predicted 85% of childhood chylothorax occurring following cardiac surgery (Buttiker *et al.* 1999). In the UK, data indicated approximately 2800 cardiac surgical procedures were undertaken per annum (PICANet 2010).

If applying these figures to estimate the number of children who developed a chylothorax following a cardiac surgical procedure in the UK, the number would be seventy children per year:

0.025 x 2800 = 70 children develop a chylothorax / year in the UK

However as previously discussed, the literature suggests that children can develop a chylothorax associated with conditions other than cardiac surgery (Allen *et al.* 1986;Beghetti *et al.* 2000;Cannizzaro *et al.* 2006;Caserio *et al.* 2010;Rocha 2007), therefore the true population was anticipated to be higher. If extrapolating the above data to include the 15% of chylothoraces occurring in children who did not have cardiac surgery, the estimated number of children who developed a chylothorax in the UK would be eighty-two children per year:

0.025 x 2800 /0.85 = 82.3 children develop a chylothorax / year in the UK

3.5.4 Data sources

Data were collected from four different data sources, one prospective and three retrospective. The inclusion criteria and the thirteen month time period for the data collection were identical. The primary, prospective data source was a questionnaire administered via the British Paediatric Surveillance Unit (BPSU) at the Royal College of Paediatrics and Child Health (RCPCH) (Data Source 1).

The three retrospective data collections relied on health record analysis from the following data sources:

- The Central Cardiac Audit Database (CCAD) – (Data Source 2)
- Hospital Episodes Statistics (HES) data – (Data Source 3)
- The Paediatric Intensive Care Audit Network (PICANet) – (Data Source 4)

CCAD and PICANet provided data on the incidence of chylothorax cases during the study period, however HES provided data on patient episodes and therefore prevalence of cases during the same time frame. HES did however provide patient identifiers including the child's NHS number, primary diagnostic category, site code for treatment and method of discharge and therefore chylothorax cases relating to the same patient episode were able to be removed.

The BPSU data was used to validate data collected from the other three sources, thus using data triangulation to cross-validate the data for both 'confirmation' and 'completeness'.

3.5.5 Incidence data

Calculation of the true incidence of chylothorax within the UK and neonatal population, was based on the BPSU data and aided by the Office for National Statistics (ONS) who provided UK population numbers for children 0 to ≤16 years, as of June 2010 (Office for National Statistics. 2011) and quarterly data on live births in the UK 2011 (Office for National Statistics. 2011). PICANet provided data on the number of children who had planned and emergency cardiac surgery undertaken in the UK during the study period and this facilitated calculation of the true incidence within this sub-group.

3.5.6 Data Source 1 – British Paediatric Surveillance Unit (BPSU)

This study was submitted and successfully adopted by the BPSU. Subsequently approval from the Research Ethics Committee (REC), the Ethics and Confidentiality Committee of the National Information Governance Board (NIGB), together with the researcher's local NHS Trust Research and Development Unit were also obtained.

3.5.6.1 Inclusion criteria

Children were included in this BPSU chylothorax surveillance study if they met the following criteria:

- Any child ≤16 years, including neonates ≥ 24 weeks gestation who developed a new chylothorax during the thirteen month period from 1st June 2010 in the UK.
- For those children who had an accumulation of lymphatic fluid in the pleural space, of which a sample was sent to the laboratory, confirmation was determined by one or more of the following criteria:
    - Triglyceride content ≥1.1 mmol/litre
    - Total cell count ≥1000 cells/microlitre
    - Lymphocyte predominance ≥80%
- Any child in whom the clinician suspects, or was awaiting confirmation of a chylothorax.
- Any child in whom the clinician had made a provisional clinical diagnosis of chylothorax, and instituted conservative management without pleural drainage e.g. Medium chain triglyceride (MCT) diet.
- Any child who had pleural drainage of cloudy / opaque fluid, consistent with a chylothorax, but no laboratory confirmation of the diagnosis sought.

3.5.6.2 Case definition

Each returned questionnaire was allocated an identification number and the individual's National Health Service (NHS), hospital number or equivalent other was used to identify any duplicate cases. Where there was duplication, the duplicate case was removed from the study. Where the case was documented

as a confirmed chylothorax, by clinical assessment or laboratory fluid analysis, the case was included in the analysis. If the confirmation of chylothorax was unclear an 'expert panel' was available to review and decide on whether the case should be included or excluded from the study.

3.5.6.3 Expert panel

The expert panel consisted of medical professionals within the lead research centre and their affiliated University. Panel members were from the following specialities:

- Neonatology
- Paediatrics
- Paediatric Intensive Care
- Microbiology
- Paediatric Cardiac Surgery
- Paediatric Cardiology

In the event, there was no need to convene this panel, however had there been a need, all identifiable information would have been removed from any data discussed.

3.5.6.4 Patient identifiable data

To allow for optimal case ascertainment, matching of cases, removal of duplicate cases, contacting notifying clinicians and achieving the research objectives, it was necessary to obtain some patient information and identifiers. These were however kept to a minimum, and their collection agreed by the National Information Governance Board (NIGB. 2010). They included the following and were requested as part of the initial information on the questionnaire:

- Diagnosis / Co-morbidity of 'chylothorax'
- NHS number or equivalent
- Hospital reference (i.e. where the infant or child was cared for)

- Date of Birth – month and year
- Gender
- Partial Postcode – first four digits
- Ethnicity
- Date of Death

Depending on the identifiable data available from each data source, a combination of the above variables were used to 'match' case. A summary of the identifiable information obtained from each data source has been provided in Table 3-2.

Table 3-2 Identifiable information obtained from each data source

British Paediatric Surveillance Unit (BPSU)	Congenital Cardiac Audit Database (CCAD)	Hospital Episode Statistics (HES)	Paediatric Intensive Care Audit Network (PICANet)
Diagnosis / Co-morbidity of 'chylothorax'	Diagnosis / Co-morbidity of 'chylothorax'	Diagnosis / Co-morbidity of 'chylothorax'	Diagnosis / Co-morbidity of 'chylothorax'
NHS Number or equivalent	X	NHS Number or equivalent	X
Hospital Identification	Hospital Identification	Hospital Identification	Hospital Identification
Date of Birth – month & year	Date of birth – month and year	Date of Birth – month and year	Date of birth – month and year
Gender	X	Gender	X
Partial Postcode – first four digits	Partial postcode – first four digits	Partial Postcode – first four digits	Partial postcode – first four digits
Ethnicity	X	Ethnicity	X
Date of Death	X	Date of Death	X

3.5.6.5 Data collection process

Data were collected via a self-administered questionnaire sent to clinicians who had reported, via the BPSU alert system, caring for a child who they judged had developed a chylothorax during the study period (Figure3-1).

3.5.6.6 Questionnaire

The aim of this surveillance questionnaire was to answer the research questions identified in Section 3.2.2, and thus build on the body of knowledge regarding chylothorax development in children (Robson 2011).

To optimise the response rate and gain maximum completion of the questionnaire significant attention was given to its development, an area which can often get overlooked in comparison to the amount of time and resources devoted to the study design, population selection and data analysis (Olsen 1998;Sushil 2010).

Ideally, comparable studies focusing on the same themes benefit from using instruments which allow data to be compared across studies and facilitate subsequent meta-analysis of data sets. This does not always occur as researchers can ignore resources available to them, or find it difficult to locate or obtain existing questionnaires (Olsen 1998). Consideration was given to existing literature and current clinical practice to support the questionnaire design. Where appropriate, parameters reported in recent chylothorax studies, including demographic data, associated conditions, management strategies and duration of intercostal pleural catheter placement, were included in the instrument (Chan *et al.* 2005), although additional variables required adding due to the heterogeneous nature of the study population.

The questionnaire was designed to enable the front page, which contained information necessary for case verification and de-duplication, to be separated

from the remaining pages that contain clinical research data and was formatted into eight sections (Appendix 6):

I. The child's details – (Demographic information)
II. Diagnosis of chylothorax – (How the diagnosis was made)
III. Location of chylothorax
IV. Mode of presentation (primary diagnosis and co-morbidities)
V. Interventional procedures
VI. Management / Treatment strategies
VII. Discharge destination or outcome from diagnosed / presumed chylothorax
VIII. Additional information

Section eight allowed for free text information to be provided by the clinician.

It was essential that the content validity of the questionnaire reflected the areas being researched and that key aspects of the study were not unintentionally excluded in the questions designed (Robson 2011). As such the questionnaire was mapped to the research aims and questions, and principal fields within the literature. Additionally, it was reviewed by medical and nursing subject-matter-experts both locally and within the BPSU which assisted with strengthening both the face and content validity (Wood 2006). This latter process provided consensual professional judgement regarding the relevance of the questionnaire content to the area being investigated, and also regarding the representativeness with which the questionnaire content addressed the area being investigated (Robson 2011). Without content validity the questionnaire would not have been fit for purpose and would not collect data that would address the research aims or questions.

The importance of ensuring the questionnaire demonstrated reliability and provided the same results when used repeatedly was key to its design. Consideration was given to the inter-rater reliability of individual questions within the questionnaire design and this was essential to ensure the results gained would be both objective and valid (Robson 2011). This was particularly

relevant in two principal areas; one in ensuring similarity in how responders categorised items and the other how they scored items. Achieving this reliability followed extensive review of the literature around questionnaire design, discussion with colleagues knowledgeable in this area of practice, and piloting the questionnaire. Any question that was not clear or produced inconsistent results was reworded and re-piloted. The re-wording of one question and re-formatting of two were required and following this consistency was present between the answers provided during the piloting, thus demonstrating inter-rater reliability.

The questionnaire contained both open-ended and closed-ended questions, with the latter offering a small number of responses from which the respondent could choose. These responses would be easily quantified and analysed (Robson 2011). Conversely, open-ended questions would allow the respondent to answer a question in their own words, which could provide depth and insight into varying aspects of care for individual cases (Robson 2011). Ensuring inter-rater reliability when analysing the content of these responses was essential if the information was to be considered objective and valid. To achieve this, two independent coders would agree the coding of the content with the application of the same coding framework. This framework would be agreed on once the questionnaires were returned and the themes identified.

The external validity, or the degree to which the findings of the study could be generalised to the target population, linked to how representative the sample was of the population (Bowling 2005). The study aimed to target a complete population or complete sub-group of a population in the UK and therefore should have had a high degree of external validity.

Bias in questionnaire design is an important issue in healthcare research and one that remains a persistent problem (Choi & Pak 2005). To collect the most accurate data, investigators must consider and ideally prevent, or minimise bias in the questionnaire design. Choi & Pak (2005) identified three main

sources of bias: the way a question is designed, the way the questionnaire as a whole is designed and how the questionnaire is administered.

Particular consideration was given to the content and wording of the questionnaire to ensure it was not misleading, and the layout was made simple and easy to record responses. Every attempt was made to ensure the questions were not leading, were short, non-ambiguous and all were directly relevant to the research questions.

The questionnaire was intended to be self-administered and therefore care was taken with the design to ensure the researcher and the responders shared the same theoretical frame and interpretation of words, phrases and concepts (McColl *et al.* 2001). The planning and piloting of the questionnaire was crucial to its success and to ensure accurate completion. Piloting of the questionnaire occurred within the researcher's own clinical environment with four clinicians who had varied experience of caring for children with a chylothorax. Two children who presented outside the study period were used for the questionnaire pilot. This process assisted in ensuring there was face validity to the questionnaire, particularly relating to an understanding of the questions and the response categories (Burgess 2001). Any ambiguity or lack of clarity to a question prompted a revision, followed by a re-confirmation with the relevant individual that face validity had been achieved. Additionally, considerable attention was given to the format and terminology used within the questionnaire to ensure the wording, sequencing, response format, placement of questions, print details and general design layout were addressed to optimise completion and return (McColl *et al.* 2001).

Response rates to questionnaires can vary greatly and are usually calculated out of the number of eligible respondents included in the study, as a percentage of the total eligible study population (Bowling 1997). The reported agreed standard for an acceptable minimum response rate varies, although there appears to be a general acceptance that a response rate of 75% and above is considered positive (Bowling 1997).

Completion rates for studies undertaken through the BPSU have been documented as high, with a response rate (proportion of orange cards completed and returned by 90 days after each mailing) of 90-95% being recorded in May 2010 (BPSU. 2010). This response rate demonstrates an encouragingly high completion rate, which could reflect a reporting system that is professionally and clinically focused and therefore highly relevant.

3.5.6.7 Missing questionnaire data

Missing questionnaire data are a common problem in surveillance research due to the large number of responses and respondents (Quinten & Raaijmakers 1999), however identifying how best to handle these data can have significant implications for the study. According to Roth *et al.* (1999) missing data can have two significant negative effects: firstly, they have a negative impact on statistical power and secondly they may result in biased estimates (Roth *et al.* 1999). Although the power of a statistical test depends on three factors; the significance level, effect size and sample size, from a practical aspect only the sample size is used to control power (Verma & Goodale 1995).

The impact of biased estimates on the study results can be multiple. Initially, central tendency may be biased upwards or downwards depending on where in the distribution the missing data appear. Furthermore, measures of dispersion may be affected depending on which part of the distribution has missing data and thirdly, missing data may bias correlation coefficients downwards (Roth *et al.* 1999).

The potential effects of missing questionnaire data depend on why the data are missing, and the technique used to deal with this situation in the analysis. Despite a researcher's best efforts, missing data could occur for a number reasons:

- An item was missed inadvertently.
- Participant fatigue, agitation or negative response to a question made completion incomplete.

- Participant deliberately omitted an item.
- Poor direction or poorly worded questions elicited no response.
- Data were collected but missed during data entry. This may be easily resolved if the original files were retrievable. (Tappen 2011)

When data are missing, establishing the quantity missing and whether the pattern of missing data are random or not, is essential. Determining how much missing data is considered too much appears inconclusive, with one study suggesting that 5-10% of missing data on one variable was not excessive (Cohen & Cohen 1983), however the implication of more than this was unclear.

Establishing whether there may be a pattern to the missing data can be categorised into data that are 'missing at random' (MAR) or data that are 'not missing at random' (NMAR). MAR data refers to the probability that a missing value is independent or unrelated to any other value or variable, such that respondents with missing values differ only by chance from those who have scored on that value. As such, results based on data from respondents with non-missing data could be generalizable to those with missing data (Little & Rubin 1987). NMAR data implies that there is a relationship between the variables with missing data and those where values are present, as such the nature of the pattern need to be understood before the results can be interpreted. To address this concern a statistical model would need to be designed (Little & Rubin 1987).

Techniques for dealing with missing questionnaire data can vary, however three of the more common approaches include; (a) deleting the variable, (b) replacing or assigning the missing variable(s) with an estimated score(s) or value(s), or (c) modelling the distribution of the missing variable(s) and estimating it, or them, based on specific parameters (Little & Rubin 1987). Following statistical advice and a review of the above information a decision was made to review whether there were any patterns to data that were missing within the questionnaire, and then either replace a missing variable with 'not known' and report this where appropriate within the study results, or identify

the individual denominator for each study question and report this within the results. Both these approaches would allow the results to be accurately presented whilst identifying any the missing data.

3.5.6.8 Data storage

As stated in Section 3.4.3, all data were stored according to the Systems Level Security Protocol (SLSP) and governed by the host Trust's Information Governance Policy.

Hard copies of the front sheet and the subsequent clinical data sheets of each questionnaire were returned to the investigator in separate stamped addressed envelopes and stored separately in locked filing cabinets with restricted access. Each questionnaire was identified by a unique British Paediatric Surveillance Unit (BPSU) case number that allowed linkage between the two. All paper-based information was stored in a locked office in the investigators hospital, not accessible to the general public and within a restricted swipe access area. Similarly the password protected electronic data were stored on the hospital server with controlled access.

3.5.7 Data Source 2 – Congenital Cardiac Audit Database (CCAD)

The NHS Information Centre (NHSIC) for Health and Social Care co-ordinates a programme of national clinical audits, which include a focus on heart disease. A sub-category within this speciality collects audit data on children using information gathered by the Central Cardiac Audit Database (CCAD), in collaboration with the Society for Cardiothoracic Surgery and the British Congenital Cardiac Association (BCCA) formerly the British Paediatric Cardiac Association.

CCAD collects information on common cardiac interventional treatments and complications, from the UK Congenital Heart Disease Centres (Table 3-3). Data were collected on children grouped according to age:

- neonates – up to 30 days old
- infants – between 31–365 days old
- children – between one and 16 years old

Table 3–3 Children's Congenital Heart Disease Centres – including Grown-up Congenital Heart (GUCH) centres, at the time of the study

Congenital Heart Disease Centres in the UK	
Alder Hey Hospital, Liverpool	Leeds General Infirmary
Birmingham Children's Hospital	Manchester Royal Infirmary
Bristol Children's Hospital	Queen Elizabeth Hospital Edgbaston, Birmingham
Cardiothoracic Centre Liverpool	Royal Brompton Hospital, London
Evelina Children's Hospital, London	Royal Hospital for Sick Children, Yorkhill, Glasgow
Freeman Hospital – Newcastle	Royal Sussex County Hospital, Brighton
Glenfield Hospital – Leicester	Royal Victoria Hospital – Belfast
Great Ormond Street Hospital For Children, London	Southampton General Hospital
Hammersmith Hospital, London	St George's Hospital – London
Harley Street Clinic, London	The Heart Hospital – UCLH – Middlesex
John Radcliffe Hospital – Oxford	University Hospital of Wales
King's College Hospital, London	

3.5.7.1 Data collection

Data submitted to CCAD is dependent on clinicians in each participating centre collecting prospective dataset information, with a data manager at each individual centre then submitting the information. Data are validated by an annual validation visit to each centre to confirm the accuracy of the information.

3.5.7.2 Data provision

For those children who developed a new chylothorax in the study period 1st June 2010 – 30 June 2011 and met the inclusion criteria, CCAD provided the following limited patient identifies:

- Diagnosis / Co-morbidity of 'chylothorax'
- Date of birth – month and year
- Partial postcode – first four digits
- Hospital Reference (i.e. where the infants and child was cared for)

These variables were then used to 'match' case with those reported from the BPSU.

3.5.7.3 Data storage

As stated in Section 3.4.3, all data were stored according to the Systems Level Security Protocol (SLSP) and governed by the host Trust's Information Governance Policy.

Data were password protected by CCAD and provided electronically. On receipt they were entered onto the password protected Trust secure server in a unique password protected database.

3.5.8 Data Source 3 – Hospital Episode Statistics (HES)

Hospital Episode Statistics (HES) are a data depository containing details of all admissions to NHS hospitals in England. Data collected includes private patients treated in NHS hospitals, patients who were resident outside of England and care delivered by treatment centres (including those in the independent sector) funded by the NHS (Department of Health 2011).

3.5.8.1 Accuracy of ICD-10 code assignment and the implications in practice

The data held by HES are prevalence cases classified according to the illnesses, diseases and/or injuries experienced by hospital patients and are recorded using the International Classification of Diseases, Tenth Revision (ICD-10), published by the World Health Organization (WHO(a) 2010). Each hospital episode experienced by an individual generates information that is collected by HES. For each episode, the patients diagnosis, procedure, treatment and outcome are recorded by the clinician in the individual's discharge summary, then filed in their health record. Following the patients discharge, this information is translated into ICD-10 codes by hospital-based clinical coders. This information is submitted to HES who then collate the data and are able to select and compare conditions both nationally through the Hospital Episode Statistics (HES) system and internationally wherever ICD-10 codes are in use.

There is however considerable debate in the literature regarding the accuracy of hospital disease coding (O'Malley *et al.* 2005;Shah *et al.* 2011;Westaby *et al.* 2007). The accurate assignment of a code is dependent on multiple factors. The coder needs to have a clear understanding of the meaning of the diagnoses and procedures (Khwaja *et al.* 2002) but also needs to be able to understand and read the patient's hospital discharge summaries, which are the main source of information for the coders. Illegible handwriting in medical records is common (Rodriguez-Vera *et al.* 2002) and can lead to coding errors, although with the increasing use of electronically generated information, this may well be reducing. Additionally, there is evidence to suggest that the level of experience of the physician completing the discharge summary can affect the accuracy of hospital coding. The number of errors was found to decline with increasing experience of the physician completing the summary (Macaulay *et al.* 1996). This may have considerable effect on the coding accuracy as junior doctors are often required to complete the discharge summaries.

The particular condition being coded also appeared to be important. Where a condition is rare, discrepancies have been reported between coders and have led to coding error (Campbell *et al.* 2001). Similarly, multiple diagnoses could

lead to error due to the subjective nature of their interpretation. Indeed, there is discord as to the accuracy of co-morbidity coding data. One study reported that coders under-reported co-morbidities compared to specialist physicians (Levy *et al.* 1999), whilst another study reported the opposite trend (Mears *et al.* 2002). This disagreement probably reflects the variation in coding accuracy between hospitals due to coder training not being centralised. Likewise, the training provided for junior doctors on the completion of discharge summaries also varies and will therefore play a role.

Codes for common conditions such as cardiovascular or respiratory illnesses (chapter codes I and J) have higher accuracy rates, with 81% accuracy for low prevalence diseases and 97% for common diagnoses (Campbell *et al.* 2001). These findings have been reiterated elsewhere (Ballaro *et al.* 2000).

Chylothorax has a specific ICD-10 code, under J90-J94, (other diseases of the pleura) (Table 3-4), specifically section J94.0 (Chylous effusion) (Table 3-5) (WHO(a) 2010).

Table 3-4 ICD-10 Classification of Chapter 'J'

ICD-10 - Chapter 'J': Diseases of the respiratory system
J00-J99 – Diseases of the respiratory system
• (J00-J06) Acute upper respiratory infections
• (J09-J18) Influenza and Pneumonia
• (J20-J22) Other acute lower respiratory infections
• (J30-J39) Other diseases of upper respiratory tract
• (J40-J47) Chronic lower respiratory diseases
• (J60-J70) Lung diseases due to external agents
• (J80-J84) Other respiratory diseases principally affecting the interstitium
• (J85-J86) Suppurative and necrotic conditions of lower respiratory tract
• **(J90-J94) Other diseases of pleura**
• (J95-J99) Other diseases of the respiratory system

Table 3-5 ICD-10 Classification of J90-J94 Conditions

(J90-J94) Other diseases of pleura
• (J90.) Pleural effusion, not elsewhere classified Pleurisy with effusion • (J91.) Pleural effusion in conditions classified elsewhere • (J92.) Pleural plaque • (J93.) Pneumothorax • (J94.) Other pleural conditions • **(J94.0) Chylous effusion** (J94.1) Fibrothorax (J94.2) Haemothorax Haemopneumothorax (J94.8) Other specified pleural conditions Hydrothorax (J94.9) Pleural condition, unspecified

However with the challenges of medical documentation, coding accuracy and the fact that chylothorax primarily presents as a co-morbidity, there was a possibility that it may not be coded at all, or it may be allocated an alternative code.

Alternative HES chapter codes for chylothorax might include:

- J94.8 – Other specified pleural conditions
- J94.9 – Pleural conditions, unspecified
- I89.8 – Other specific non-infective disorder of the lymphatic vessels and lymph node
- I89.9 – Non-infective disorder of lymphatic vessels and lymph node unspecified

When investigating the process of how HES codes are applied to patient conditions, two key manuals were found to be available to the coders to guide

their decision making practices (WHO(a) 2010;WHO(b) 2010), and to direct them to the correct HES code(s) to be applied for each diagnoses. When searching for 'chylothorax' in the ICD-10 Alphabetical Index (WHO(b) 2010), the HES code I89.8 (non-infective disorder of lymphatic vessels and lymph nodes, unspecified) was identified as the code to be used for this condition. However if the term 'chylous' was being sought, the coder would be directed to 'see condition', which would lead them to the primary reason for the individuals admission and therefore no coding of the chylothorax would be made. Alternatively however, if the chylothorax was documented in the individuals patient notes as a 'chylous effusion', the coders would be directed to use the ICD-10 Alphabetical Index (WHO(b) 2010) to focus on 'Effusion' and then find the term 'chylous', in which case the HES code J94.0 would be identified as the code to documented. These discrepancies add to the challenges of accurate ICD-10 coding and may also have significant financial implication for institutions depending on the tariff level applied to these codes.

Consideration of the above possible inconsistencies in data documenting and recording were therefore reflected on when applying to HES for the data on any child who had developed a chylothorax during the study period. A request was made within the HES search strategy to include a review of all five of the above specific codes. The search request included a review of all datasets for the identification of any child who met the chylothorax study inclusion criteria (Section 3.5.6.1) where chylothorax had been identified as either a primary or secondary code or co-morbidity. This would allow for a broad search to be made which would help enhance case ascertainment and provide the optimal chance of individuals being identified.

When reviewing the publically available data within HES and focusing on the number of cases of children ≤16years who were recorded as having diagnoses or procedures that were coded within the above specific codes, numbers were small. These publically available data were only available in specific age categories of 0-14 years and 15-59 years, hence not identical to the study age group. However, data for the former category did provide an impression of the likely number of cases (Table 3-6).

Data were available to view over the past thirteen years, with the number of cases identified under the more specific chylothorax code of J94.0 averaged at 8.3 cases per year, with an increased average of 26.7 children being identified under the more general code of I89.8. Although this latter coding group has a higher number of children recorded within it, the specifics of the conditions included within this category provided no additional information other than the category and a sub-category stating 'Disease of lymphatic vessels, not otherwise specified (NOS). Of interest was the fact that all chylothorax cases identified within the study host site were noted to have been recorded under the specific code I89.8, rather than the more precise code J94.0. This is likely to be reflective of the terminology used within the hospital and amongst clinicians documenting the co-morbidity in the child's discharge summary as a chylothorax, rather than a chylous effusion and hence the coders applying this term to the coding process, and also of the training and education these staff have received. This is an inconsistency that could exist in other hospitals and as such potentially raises additional concerns regarding the accuracy of the data provided for this study, and also has wider implications regarding the accuracy of data HES provide to other sources or studies.

Although the accuracy of HES coding can clearly be debated, it does appear to have improved with time (Stausberg *et al.* 2008), which may suggest that accuracy has improved since some of the above studies were completed. The ICD-10 system has now been in effect since 1999 and a 4-11% increase in accuracy was demonstrated over a two-year period across several hospitals (Dixon *et al.* 1998) which may reflect coders becoming better acquainted with the system. However, many of the studies presented were based on the ICD-9 rather than ICD-10 system and so comparison of accuracy between the studies is problematic.

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Table 3-6 Overview of HES data 1998-2011 for chylothorax (data published for age range 0-14 years)

YEAR	J94.0 Chylous effusion	J94.8 Other specified pleural conditions	J94.9 Pleural condition unspecified	I89.8 Other spec-non-infective disorder of lymphatic vessels and lymph node	I89.9 Non-infective disorder of lymphatic vessels and lymph node unspecified	Year total
2010-2011	12	3	0	33	7	**55**
2009-2010	19	12	0	23	11	**65**
2008-2009	14	14	2	35	15	**80**
2007-2008	5	11	0	26	13	**55**
2006-2007	19	6	1	31	13	**70**
2005-2006	9	4	3	13	7	**36**
2004-2005	9	2	0	30	8	**49**
2003-2004	9	5	0	33	6	**53**
2002-2003	2	6	0	33	7	**48**
2001-2002	2	1	3	18	16	**40**
2000-2001	7	1	3	12	13	**36**
1999-2000	1	3	2	33	8	**47**
1998-1999	0	2	0	27	9	**38**
Specific Code Total	**108**	**70**	**14**	**347**	**133**	

Despite methodological issues associated with using hospital coding in research, hospital codes constitute the best available dataset of diagnoses in hospital and continue to be used widely for insurance purposes, reimbursement, to map diseases worldwide and to plan and fund services (Austin *et al.* 2002;Dixon *et al.* 1998;Stausberg *et al.* 2008). They are also widely available, are relatively cost-effective to collect and are representative of the entire population (Movig *et al.* 2003). In this study, triangulation of the data would allow coding accuracy for this condition to be estimated.

3.5.8.2 Data collection

As with the CCAD data, the availability of information from HES was dependent on individual clinicians having identified a child who developed a chylothorax and then the coding staff accurately coding them, prior to submitting their Hospital data to HES.

3.5.8.3 Data provision

Applying to obtain HES data was a component of both the Research Ethics Committee (REC) and the National Information Governance Board (NIGB. 2010) applications. The request included the provision of the following limited identifies for the study period, for any child with a HES chapter code of J94, J94.8, J94.9, I89.8 or I89.9 recorded in their primary or secondary coding or as a co-morbidity:

- Diagnosis / co-morbidity of 'chylothorax'
- NHS Number or equivalent
- Site Code of Treatment - Hospital Reference (i.e. where the infant or child was cared for)
- Date of Birth – month and year
- Gender
- Partial Postcode – first four digits
- Ethnicity
- Method of discharge

Data were reviewed and where multiple entries were present for the same child, reflecting the prevalence of cases collected by HES, these were reduced to a single entry based on the child's discharge method. Therefore, if a child had multiple treatment episodes recorded with a discharge method of 'not applicable: patient still in hospital', the case was reduced to one entry where the discharge method was either 'discharged on clinical advice or with clinical consent', or 'died'. These variables were then 'matched' to case with those reported from the BPSU.

3.5.8.4 Data storage

All data were stored according to the Systems Level Security Protocol (SLSP) and governed by the host Trust's Information Governance Policy.

Data were received from HES by Royal Mail 'Special Delivery ™', on two password protected CDs. Data were entered onto the password protected Trust secure server in a unique password protected database.

3.5.9 Data Source 4 – Paediatric Intensive Care Audit Network (PICANet)

PICANet is a national clinical audit co-ordinated by the Universities of Leeds and Leicester and supported by the Health Quality Improvement Programme (HQIP). It provides a clinical audit of paediatric intensive care (PIC) activity in the UK and Republic of Ireland (RoI) which aims to improve patient outcomes by providing information on delivery of care to critically ill children, and an evidence base for clinical governance. Participating units are those listed in Table 3-7.

PICANet was first established in 2001 and works in close collaboration with members of the Paediatric Intensive Care clinical community. Their specific objectives include identifying best practice, monitoring supply and demand, monitoring and reviewing outcomes of treatment episodes, facilitating

strategic health care planning, quantifying resource requirements and studying the epidemiology of critical illness in children (PICANet 2010).

The network also aims to facilitate the auditing of the Paediatric Intensive Care Society (PICS) Standards (PICS 2010) for PIC including both clinical and patient, or parent reported outcome measures.

Table 3-7 Hospitals participating in PICANet Audit Data Collection (as of July 2011)

Location	Unit
Belfast	The Royal Group of Hospitals & Dental Hospital HSS Trust
Birmingham	Birmingham Children's Hospital NHS Foundation Trust
Brighton	Brighton & Susses University Hospitals NHS Trust
Bristol	University Hospitals Bristol NHS Foundation Trust
Cambridge	Cambridge University Hospitals NHS Foundation Trust
Cardiff	Cardiff and Vale NHS Trust
Dublin	Our Lady's Children's Hospital Crumlin Children's University Hospital, Temple Street
Edinburgh	NHS Lothian - University Hospitals Division
Glasgow	NHS Greater Glasgow and Clyde - Women and Children's Division
Hull	Hull & East Yorkshire Hospitals NHS Trust
Leeds	Leeds Teaching Hospitals NHS Trust
Leicester	University Hospitals of Leicester NHS Trust
Liverpool	Royal Liverpool Children's NHS Trust
London	St Bartholomew's' and The London NHS Trust Great Ormond Street Hospital for Children NHS Trust Guys' & St Thomas' NHS Foundation Trust King's College Hospital NHS Trust Royal Brompton & Harefield NHS Trust St George's Healthcare NHS Trust St Marys' NHS Trust The Harley Street Clinic
Manchester	Central Manchester & Manchester Children's University Hospitals NHS Trust
Middlesbrough	South Tees Hospitals NHS Trust
Newcastle upon Tyne	Newcastle upon Tyne Hospitals NHS Foundation Trust
Nottingham	Nottingham University Hospitals NHS Trust

Location	Unit
Oxford	Oxford Radcliffe Hospitals NHS Trust
Sheffield	Sheffield Children's NHS Foundation Trust
Southampton	Southampton University Hospitals NHS Trust
Stoke	University Hospital of North Staffordshire NHS Trust

The national PICANet dataset continuously records details of admission, discharge, diagnoses, medical history, physiology, interventions and outcome using 'Read Codes' (Clinical Terms version 3) (NHS Connecting for Health 2013). The outcome information is adjusted by 'case-mix' to provide reliable evidence on patients' outcomes for clinicians, managers and patients. From 2007 the 'case-mix' adjustment tool has been the Paediatric Index of Mortality 2 (PIM2). Data quality processes including feedback between PICANet and the PIC Units, and Unit validation visits to ensure dataset are accurate, robust and complete, are all undertaken by PICANet.

Read codes are a computerised coding thesaurus used by some NHS clinicians to code and record relevant information linked to a patient's clinical admission. They enable a summary of the health events of the patient to be coded and stored in a computer system and contain mapping fields and tables which can be cross referenced to ICD-10 codes (NHS Connecting for Health 2013). The main benefit of using Read codes rather than ICD-10 codes relates to the former systems ability to react faster and reflect immediate changes and developments in clinical practice and therefore provide more detailed accurate clinical data. An example of this would be the identification of the H1N1 virus in 2009 which was able to be allocated a Read code immediately, whilst the ICD-10 coding system was less reactive, requiring a more staged approach to recording.

PICANets decision to use Read Codes rather than ICD-10 codes relates to their reactivity to changes in clinical practice and hence their accuracy. However the availability and use of both Read codes and ICD-10 codes within the NHS and between the data sources accessed for this study, creates the potential for

inconsistencies in the reporting and coding of chylothorax which could have impacted on the accuracy of reported case numbers and incidence rates.

3.5.9.1 Data collection

The data collected by PICANet is owned by those units who submitted it, therefore any provision of information to a third party required agreement from both the relevant PICU and PICANet.

3.5.9.2 Data provision

For the twenty-six units that agreed to release their data, PICANet forwarded the study investigator the following retrospective patient identifiable data:

- Diagnosis / Co-morbidity of 'chylothorax'
- Date of birth – month and year
- Partial postcode – first four digits
- Hospital Reference (i.e. where the infant or child was cared for)

3.5.9.3 Data storage

All data were stored according to the Systems Level Security Protocol (SLSP) and governed by the host Trust's Information Governance Policy.

Data were password protected by PICANet and provided electronically. On receipt they were entered onto the password protected Trust secure server in a unique password protected database.

3.5.10 Data management

Data analysis was undertaken using IBM® SPSS® v20 Statistical Software (Statistical Package for Social Sciences). Thirty-five (20%) of the BPSU questionnaires were double entered to assess and reduce error, and data were

cleaned by checking for outliers and missing data by the use of frequency tables, histograms and scatterplots.

3.5.11 Data analysis

Data for each of the four data sources were analysed using descriptive statistics and measures of central tendency. Categorical data are presented as percentages and counts. Due to a lack of normal data distribution, the median with the interquartile ranges offer a clearer and more accurate representation of the data, however the mean with 95% confidence intervals are also presented for the demographic characteristics and clinical features of the children, age at diagnosis linked to their primary diagnosis and the length of stay for treatment strategies. This facilitates quantitative comparisons with similar data reported in the literature.

Within the BPSU data, Fisher exact test or Spearman rho correlational analysis were undertaken to assess whether any difference(s) or relationship(s) existed between key categorical variables. The probability of the child surviving was then assessed through logistical regression analysis.

A sub-group analysis was undertaken within the BPSU data, of those children who developed a chylothorax following cardiac surgery. A second sub-analysis was undertaken of the 'match' cases identified between the HES data and those children reported via the BPSU to have developed a chylothorax in England.

Free text data documented within the BPSU questionnaire were analysed and grouped by content.

The data are presented in the following chapter reporting the incidence of chylothorax in UK children and outlining the population size, describing the

demographic characteristics and clinical features of children, their associated primary diagnoses, treatment strategies, length of stay and discharge destination or outcome. For ease of reading the findings, text, tables and figures are presented sequentially throughout the chapter and where tables are relevant to more than one section, they have been cross-referenced.

4. Findings

4.1 British Paediatric Surveillance Unit (BPSU) Data

4.1.1 Case identification

Case identification and data collection took place over a thirteen month period from 1st June 2010 to 30th June 2011. This time frame reflects the study period advocated by surveillance studies supported by the BPSU, which allows for consideration of any seasonal effects related to the study population, optimises the sample number in rare conditions and provides a month to embed the study into practice.

Clinicians reported caring for 253 children who developed a chylothorax and questionnaires were sent out to each of these. 219 (86.5%) questionnaires were returned, of which 173 cases met the eligibility criteria for inclusion (Figure 4-1).

Figure 4-1 illustrates the case identification process. Those described as 'unable to follow-up' refer to cases where no completed questionnaire was received from the reporting clinician. After their initial reporting of the case, clinicians were sent up to six reminder emails over a five-month period. If no response was obtained four weeks after the final reminder, the case was classified as 'unable to follow-up'. 17 (50%) of the 'unable to follow-up' cases were from one hospital, with the remaining 17 cases being reported from ten different hospitals. Thirteen 'error cases' reported within those 'ineligible', were cases that either did not meet the age criteria, occurred outside the study period, or were cases reported in error to the study investigator by the BPSU.

Data were ultimately obtained on one hundred and seventy-three children.

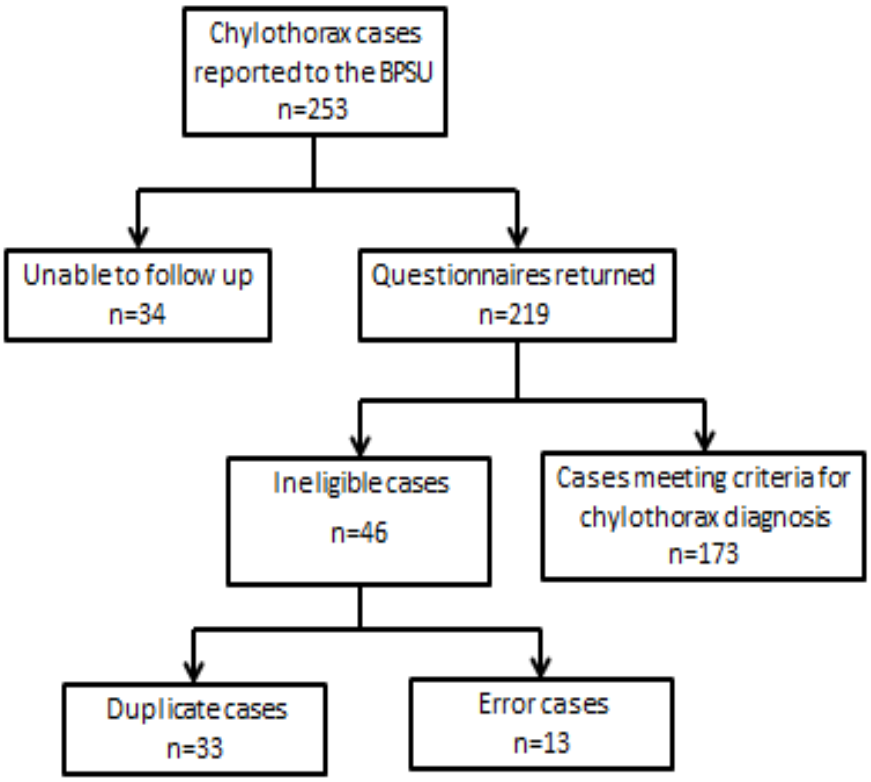


Figure 4-1 BPSU Case identification process

The following results section is split into ten subsections based on the key research questions.

I. Demographic characteristics of the population
II. Incidence
III. Diagnosis of the chylothorax
IV. Diagnostic groups of the children who developed a chylothorax
V. Hospitals providing care for children who develop a chylothorax
VI. Interventional procedure(s) undertaken prior to a chylothorax developing
VII. Length of child's hospital stay and their discharge destination or outcome
VIII. Exploratory analysis of data

IX. Qualitative data analysis
X. Sub analysis of children who developed a chylothorax following cardiac surgery.

Tables are located within the text for ease of reference, however may be referred to by their 'Table, Section Number and Page Number' if referred to in more than one section.

4.1.2 Demographic characteristics of the population

The following section describes the demographic and clinical data of the population, with Table 4-1 and Table 4-2 providing an overview. The median age was 2 months and 94 (54.5%) were male. It can be seen that n=140 (81%) were from a white ethnic background, although a range of ethnicities were represented.

Table 4-1 Gender and ethnicity of BPSU study population

Demographic characteristic		Number (%)	UK ethnicity 2001/02 (%)	England & Wales 2011 (%)
Gender:	Male	94 (54.5)		
Ethnicity:	White	140 (81)	93	86
	Asian or Asian British	20 (11.5)	3.9	7.5
	Black or Black British	7 (4)	2	3.3
	Mixed	3 (1.7)	0.3	2.2
	Other	3 (1.7)	0.8	1

(Ethnicity percentage comparisons provided from Office for National Statistics census data 2001/2 and 2011)

The data were not normally distributed and whilst 16 months was the mean age at which children were diagnosed with a chylothorax, the median age was 2 months. The ages of the children ranged from 27.5 weeks to 174 months (14.5 years) (IQR 14), which reflected the study's eligibility criteria (≥24 weeks to ≤16 years) and was consistent with other published data (Beghetti *et al.* 2000;Caserio *et al.* 2010;Chan *et al.* 2005;Rocha *et al.* 2006), although these

studies only focused on children who had developed a chylothorax following cardiac surgery or in their neonatal period. 74% (n=128) of the population were infants ≤11 months of age.

Table 4-2 Clinical features, median, mean and confidence intervals

Clinical feature	Median (range) [IQR]	Mean [95% CI for mean]
Birth Weight if ≤1 yr (kgs)	2.8 (0.78 – 4.40) [0.96]	2.74 [2.59-2.89]
Weight at diagnosis (kgs)	4.8 (1.50 – 51.40) [5.29]	7.34 [6.22-8.46]
Gestational age if ≤1 yr at presentation of chylothorax (wks)	38 (27.57 – 41.57) [4.15]	37.0 [36.37-37.54]
Age at diagnosis (months)	2 (0 – 174) [14]	16.22 [11.56-20.88]

Those children who presented with a chylothorax under one year of age, n=119 (69%), had a median gestational age of 38 weeks with a range from 27.6 weeks to 41.6 weeks (IQR 4.15). Although the gestational mean for this sub-group fell within the time period considered to be a 'term' pregnancy (≥37 to ≤42 weeks gestation), the population was skewed by n=46 (38.5%) 'preterm' infants, ≤37 weeks gestation. The birth weight of the sample was however normally distributed with a mean of 2.74kgs (range 0.78kgs to 4.4kgs), (95% CI 2.59 -2.89). The median weight of the entire BPSU population at diagnosis of the chylothorax was 4.8kgs (range 1.5kgs to 51.4kgs) (95% CI 6.22-8.46).

A number of the children were noted to have a congenital disorder n=30 (17.3%), with Down syndrome (n=18, 10.4%) and Noonan syndrome (n=7, 4%) being the most commonly reported (Figure 4-3).

Table 4-3 Children reported as having a congenital disorder

Congenital disorder	Number (%) (n=173)
Down syndrome	18 (10.4)
Noonan syndrome	7 (4.0)
DiGeorge syndrome	2 (1.1)
Apert syndrome	2 (1.1)
Turner syndrome	1 (0.6)
Total	**30 (17.3)**

4.1.3 Incidence

4.1.3.1 Incidence of chylothorax within the United Kingdom (UK) child population

Having analysed and reviewed the above data, the UK incidence of chylothorax in children was reviewed within three key categories. Firstly as a total incidence for the UK population and then within the two most commonly associated clinical diagnostic groups; following cardiac surgery and those with a neonatal abnormality.

Calculation of the UK incidence of chylothorax, was based on the BPSU data and was assisted by the Office for National Statistics (ONS) who provided UK population data for children 0 to ≤16years, as of June 2010 (Office for National Statistics. 2011), (Table 4-4).

From the BPSU (UK) data, the incidence of chylothorax in children was calculated as follows:

- Incidence = 173/12,365,900 = 0.000014 x 100% = 0.0014%
  (1.4 in 100,000)

This slightly increased when looking solely at the incidence in the infant age group (≤12 months) and was calculated as follows:

- Incidence = 128/795,200 = 0.00016 x 100% = 0.016%.
  (1.6 in 100,000)

This infant incidence mirrored the 0.01% incidence reported by Rocha *et al.* (2006) in their multi-centre Portuguese study of neonates and pre-term infants.

Table 4-4 Office for National Statistics - Mid-2010 Population Estimates for the United Kingdom. Data for children from birth to 16 years, (Table1)

Age groups	Age by year	Population by year (Thousand)	Total population for age group (Thousand)
0-4 years	0	795.2	
	1	784.7	
	2	788.6	
	3	756.5	
	4	733.5	
Total			**3,858.4**
5-9 years	5	718.7	
	6	709.0	
	7	684.9	
	8	666.3	
	9	667.6	
Total			**3,446.4**
10-14 years	10	683.3	
	11	703.1	
	12	715.5	
	13	734.8	
	14	730.2	
Total			**3,566.9**
15-16 years	15	736.4	
	16	757.8	
Total			**1,494.2**
Grand Total			**12,365.9**

Findings

Calculation of England's incidence of chylothorax was based on the HES data and assisted by the Office for National Statistics (ONS) provided the appropriate population estimates, based on the 2011 census (Office for National Statistics. 2012) (Table 4-5).

The incidence was calculated as follows:

- HES Data (England only).
    - Incidence = 276/10,673,600 = 0.000026 x 100% = 0.0026% (2.6 in 100,000)

Table 4-5 Office for National Statistics - Mid-2011 Population Estimates for England; based on the results of the 2011 Census. Data for children from birth to 16 years (Table4)

Age groups	Age by year	Population by year (Thousand)	Total population for age group (Thousand)
0-4 years	0	679.1	
	1	669.9	
	2	661.9	
	3	669.5	
	4	648.4	
Total			**3,328.7**
5-9	5	635.9	
	6	608.3	
	7	597.7	
	8	579.8	
	9	568.5	
Total			**2,990.1**
10-14	10	583.2	
	11	599.0	
	12	617.3	

Age groups	Age by year	Population by year (Thousand)	Total population for age group (Thousand)
	13	625.1	
	14	642.7	
Total			**3,067.4**
15-16	15	643.8	
	16	643.6	
Total			**1287.4**
Grand Total			**10673.6**

4.1.3.2 Chylothorax incidence associated with cardiac surgery

PICANet provided data on the number of children who had both planned and emergency cardiac surgery undertaken in the UK during the study period, n=3660. This information was used to calculate the incidence of chylothorax that developed following cardiac surgery. The entire population n=3660 was used as the denominator for the BPSU data, however cases from Wales, Scotland and Northern Ireland, n=270, were removed to establish the denominator for the HES data incidence, hence this denominator was n=3390.

Both BPSU and HES data reported 113 children who developed chylothorax following cardiac surgery (Table 4-6 and Table 4-56). The incidence was therefore calculated as follows:

- BPSU (UK).
  Incidence = 113 / 3660 = 0.0308 x 100% = 3.1% (3,100 in 100,000)

- HES (England).
  Incidence = 113 / 3390 = 0.0333 x 100% = 3.3% (3,300 in 100,000)

These results reflect the 3.2% average incidence currently reported and discussed in the literature (Section 2.4. Table 2-1).

Table 4-6 Cardiac surgical cases undertaken in the UK June 2010 - June2011- data provided by PICANet

(Definitions of the hospital categories are presented in Section 4.1.6)

Hospital	Strategic Health Authority (SHA)	Planned cardiac surgery	Unplanned cardiac surgery	Total
Tertiary Cardiac Hospital 9	7	481	30	511
Tertiary Cardiac Hospital 5	7	391	3	394
Tertiary Cardiac Hospital 6	2	391	6	397
Tertiary Cardiac Hospital 7	7	384	2	386
Tertiary Cardiac Hospital 1	5	338	33	371
Tertiary Cardiac Hospital 2	3	298	6	304
Tertiary Cardiac Hospital 10	9	275	5	280
Tertiary Cardiac Hospital 3	10	269	7	276
Tertiary Cardiac Hospital 4	12	234	12	246
Tertiary Cardiac Hospital 8	1	200	6	206
Tertiary Cardiac Hospital	7	151	0	151
Tertiary Cardiac Hospital	4	129	3	132
Tertiary Combined Hospital	13	17	3	20
Tertiary Combined Hospital	2	5	5	10
Tertiary Combined Hospital	4	4	3	7

Hospital	Strategic Health Authority (SHA)	Planned cardiac surgery	Unplanned cardiac surgery	Total
Tertiary Combined Hospital	7	4	1	5
Tertiary Combined Hospital	6	3	1	4
Tertiary Combined Hospital	9	3	0	3
Tertiary Combined Hospital	7	2	2	4
Tertiary Combined Hospital	7	2	1	3
Tertiary Combined Hospital	11	1	0	1
Tertiary Combined Hospital	1	1	0	1
Tertiary Combined Hospital	7	1	0	1
Tertiary Combined Hospital	3	1	1	2
Tertiary Combined Hospital	9	0	1	1
Tertiary Combined Hospital	12	0	3	3
Total		**3585**	**134**	**3719**
Total (children ≤ 16yrs)				**3660**

* Total Case numbers included 59 children ≤ 16yrs and therefore outside the study age

Findings

As a result of the poor data submission to CCAD it was not possible to calculate the incidence of children who developed a chylothorax from this data source.

4.1.3.3 Chylothorax incidence associated with a neonatal condition

Finally, calculation of the incidence of chylothorax associated with a neonatal condition, either congenital or 'other' (non-cardiac) for both the BPSU and HES data, were based on the Office for National Statistics (ONS) data on the number of UK live births for the study period (Office for National Statistics. 2011) (Table 4-7). The incidence rates were calculated as follows:

- BPSU (UK).
  Incidence = 34 (**Error! Reference source not found.**) / 876,800 = 0.00004
  100% = 0.004%
  (4 in 100,000)

- HES (England).
  Incidence=55 (Table 4-56) /746,600 = 0.00007 x 100% = 0.007%
  (7 in 100,000)

Table 4-7 Office for National Statistics, Quarterly data: Live births, UK and constituent countries (2011).

Year and quarter		Number of live births (thousands)				
		United Kingdom	England	Wales	Scotland	Northern Ireland
2010	**June (only)**	65.7	55.9	2.9	4.9	2.2
	September	207.1	176.5	9.2	14.9	6.4
	December	207.3	177.2	9.3	14.5	6.2
2011	**March**	196.3	166.3	8.7	14.6	6.7
	June	200.4	170.7	8.8	14.7	6.2
	Total	**876.8**	**746.6**	**38.9**	**63.6**	**27.7**

4.1.3.4 Summary of incidence data

The number of children who developed a chylothorax in England and the UK was small. Indeed the overall incidence of chylothorax development in the UK child population was 0.0014%, (1.4 in 100,000), with a slight increase when focusing specifically on cases occurring in England, 0.0026% (2.6 in 100,000).

When reviewing the incidence of chylothorax development in children following cardiac surgery, the UK incidence was 3.1% (3,100 in 100,000), rising marginally to 3.3% (3,300 in 100,000) in England. This slightly higher incidence in England reflects the fact that children's cardiac surgery for Wales in undertaken in England.

Congenital conditions were the second most common diagnostic group although the incidence rate in the UK was extremely small at 0.004% (4 in 100,000), rising slightly to 0.007% in England (7 in 100,000).

4.1.4 Diagnosis of the chylothorax

Clinicians were asked to respond to each of nine statements relating to how they suspected and/or confirmed chylothorax diagnosis. Additionally they were asked to identify any other method that had been applied.

The most common method for confirming the development of a chylothorax was by laboratory analysis of pleural fluid indicating a triglyceride content of ≥1.1 mmol/litre, n=114 (66%) (Table 4-8). However, other diagnostic techniques were used (Table 4-8), with clinicians frequently using more than one method. Within the 'Other' section, in n=15 cases (8.5%) clinicians identified chylomicron levels in the pleural fluid had been requested and reported. No other test was identified as having been applied to assist in the diagnosis of chylothorax.

Table 4-8 Method(s) use to diagnosis the chylothorax

Diagnostic category	Diagnosis of a chylothorax Number (%)
Laboratory confirmation – triglyceride content of pleural fluid ≥1.1 mmol / litre*	114 (66)
Underlying clinical diagnosis of the child*	52 (30)
Timing of the development of the chylothorax*	44 (25.5)
Laboratory confirmation – lymphocyte predominance in pleural fluid ≥80%*	43 (25)
Pleural drainage was cloudy but no laboratory confirmation sought*	36 (21)
Speed of accumulation of the chylothorax*	35 (20)
Laboratory confirmation – total cell count of pleural fluid ≥1000 cells / microliter*	34 (20)
Clinical Suspicion of Chylothorax – No pleural drain Inserted*	26 (15)
Pleural Effusion on XRay or Ultrasound – No Pleural drain Inserted*	25 (14.5)
Other – Chylomicrons	15 (8.5)

*n=173 (100%) possible for each diagnostic category

4.1.5 Diagnostic grouping of children reported to have developed a chylothorax

Clinicians were requested to identify the primary diagnosis and other additional diagnoses of the child they were reporting as having developed a chylothorax. These were categorised into two groups using the same eight diagnostic categories (Table 4-9). The majority of the population n=113 (65.3%) had had cardiac surgery. Additional diagnoses were most commonly linked to a neonatal or neonatal congenital problem n=34 (19.5%). Trauma was not identified as a primary condition linked to chylothorax development within this population, although it was identified within the additional diagnoses, n=4 (2.5%).

Table 4-9 Primary and subsequent diagnoses of children who developed a chylothorax

Primary diagnosis	Number (%) (n=173)
Cardiac Surgical	113 (65.3)
Neonatal Congenital	22 (12.5)
Surgery (non-cardiac)	14 (8)
Neonatal Other	12 (7)
Cardiac Medical	4 (2.3)
Not Known	4 (2.3)
Medical (non-cardiac)	3 (2)
Oncology / Haematology	1 (0.5)
Trauma	0 (0)
Additional diagnoses	**Number (%) (n=173)**
None	147 (85)
Neonatal Congenital	8 (4.5)
Neonatal Other	6 (3.5)
Trauma	4 (2.5)
Cardiac Medical	3 (1.7)
Cardiac Surgical	3(1.7)
Medical (non-cardiac)	1 (0.5)
Surgery (non-cardiac)	1 (0.5)
Oncology / Haematology	0 (0)

Only n=26 (15%) of clinicians reported any additional associated condition for the child, with none reporting a third.

Table 4-10 shows the mean age at diagnosis (months) for children in each of the primary diagnostic categories, together with the minimum and maximum months of age for each category. In the neonatal categories diagnosis of a chylothorax was made at approximately a month of age, with children in all other categories being diagnosed with chylothorax at five months or older. The cardiac medical diagnostic group were the oldest group of children, with a

mean age of just over five years, all had a primary diagnosis of cardiomyopathy. Figure 4-2 provides a graphical representation of these data.

Table 4-10 Primary diagnostic category and age at chylothorax diagnosis

Primary diagnostic category	Number (%) (n=173)	Age at diagnosis (months)
		Mean [minimum-maximum]
Cardiac Surgical*	113 (65.3)	19.55 [0-168]
Neonatal Congenital*	22 (12.5)	0.32 [0-3]
Surgery (non-cardiac)*	14 (8)	17.71 [0-172]
Neonatal Other*	12 (7)	0.33 [0-3]
Cardiac Medical*	4 (2.3)	62.25 [0-174]
Not Known/ Other**	4 (2.3)	n/a
Medical (non-cardiac)	3 (2)	5.0 [2-8]
Oncology / Haematology**	1 (0.5)	n/a
Trauma	0 (0)	0

*includes pre-term infants and infants ≤ one month of age.
**includes pre-term infants 36-39 weeks gestation

(Box plots showing median and interquartile ranges, whiskers denote range of values, outliers as * or °)

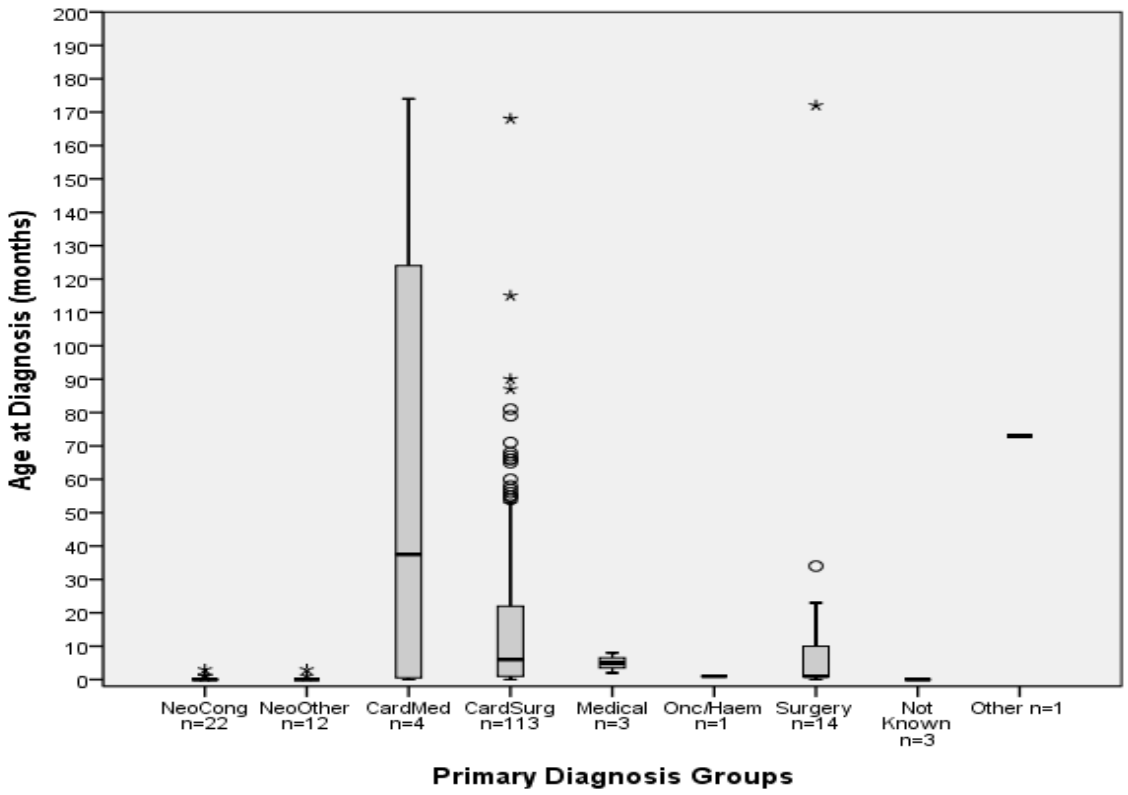


Figure 4-2 Primary diagnostic categories and age at chylothorax diagnosis

In summary, development of a chylothorax was most commonly reported in relation to cardiac surgery n=113 (65.3%) and neonatal congenital conditions n=22 (12.5%). The majority of clinicians diagnosed the chylothorax through laboratory confirmation of triglyceride levels within the pleural fluid ≥1.1mmol/litre, n=114 (66%). Infants who developed a chylothorax in the neonatal period had a mean age of one month at diagnosis, whilst children who developed the condition following cardiac surgery had a mean age of nineteen months of age.

4.1.6 Care setting for children who developed a chylothorax

Forty-nine hospitals across the United Kingdom reported caring for children who developed a chylothorax within the study period. These hospitals were classified into five categories according to the services they provide, and are defined below.

Hospital categories:

- Tertiary Cardiac – Hospital with tertiary paediatric cardiac intensive care facilities, +/- general paediatric intensive care facilities.
- Tertiary Neonatal – Hospital with tertiary neonatal intensive care facilities.
- Tertiary Combined – Hospital with tertiary neonatal, and general paediatric intensive care facilities, but no tertiary paediatric cardiac intensive care facilities.
- Tertiary Other – Hospital with tertiary clinical specialities e.g. orthopaedics or burns, but with no tertiary neonatal or paediatric intensive or cardiac care facility.
- District General Hospital (DGH) – All other hospitals.

Each hospital category was mapped to their corresponding Strategic Health Authority (SHA) which represents a region of the UK and these are shown in Table 4-11. Children were treated in all SHAs across the UK although there was geographic variation in the number of children cared for by each, ranging from 1-34.

Table 4-11 BPSU data: Category of hospital caring for the child and its corresponding Strategic Health Authority (SHA)

Strategic Health Authority (SHA)	Hospital category Number of cases (%)					
	Tertiary Cardiac	Tertiary Neonatal	Tertiary Combined	Tertiary Other	District General Hospital	Total
SHA 1	8 (4.6)	1 (0.6)	1 (0.6)	0 (0)	1 (0.6)	**11 (6.4)**
SHA 2	10 (5.8)	1 (0.6)	0 (0)	0 (0)	1 (0.6)	**12 (7.0)**
SHA 3	22 (12.7)	1 (0.6)	0 (0)	0 (0)	4 (2.3)	**27 (15.6)**
SHA 4	2 (1.2)	0 (0)	2 (1.2)	0 (0)	0 (0)	**4 (2.3)**
SHA 5	31 (17.9)	3 (1.7)	0 (0)	0 (0)	0 (0)	**34 (19.6)**
SHA 6	0 (0)	1 (0.6)	0 (0)	0 (0)	1 (0.6)	**2 (1.2)**
SHA 7	23 (13.3)	2 (1.2)	3 (1.7)	4 (2.3)	2 (1.2)	**34 (19.6)**
SHA 8	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.6)	**1 (0.6)**
SHA 9	4 (2.3)	1 (0.6)	1 (0.6)	0 (0)	0 (0)	**6 (3.4)**
SHA 10	15 (8.7)	2 (1.2)	0 (0)	0 (0)	1 (0.6)	**18 (10.4)**
SHA 11	0 (0)	1 (0.6)	2 (1.2)	0 (0)	1 (0.6)	**4 (2.3)**
SHA 12	14 (8.0)	2 (1.2)	0 (0)	1 (0.6)	2 (1.2)	**19 (11.0)**
SHA 13	0 (0)	1 (0.6)	0 (0)	0 (0)	0 (0)	**1 (0.6)**
Total	**129 (74.5)**	**16 (9.3)**	**9 (5.2)**	**5 (2.9)**	**14 (8.1)**	**173 (100)**

The majority of children, n=145 (83.8%) were cared for in either a tertiary cardiac or neonatal hospital, with the majority of these being in tertiary cardiac centre, n=129 (74.5%), which is reflective of the high proportion of the children who developed a chylothorax following cardiac surgery and who require initial management in intensive care.

The principal hospitals that reported caring for the majority of children who developed a chylothorax n=127 (73.5%) are identified in (Table 4-12). All are tertiary cardiac hospitals which is reflective of the cardiac surgery diagnoses, where children require paediatric intensive care facilities and expertise after their operative procedure.

Table 4-12 Key hospitals reporting caring for children who developed chylothorax

Hospitals	SHA	Reported cases
Tertiary Cardiac Hospital 1	5	31
Tertiary Cardiac Hospital 2	3	22
Tertiary Cardiac Hospital 3	10	15
Tertiary Cardiac Hospital 4	12	14
Tertiary Cardiac Hospital 5	7	10
Tertiary Cardiac Hospital 6	2	10
Tertiary Cardiac Hospital 7	7	8
Tertiary Cardiac Hospital 8	1	8
Tertiary Cardiac Hospital 9	7	5
Tertiary Cardiac Hospital 10	9	4
Other (39 Hospitals)		46
Total		**173**

4.1.7 Treatment strategies applied to manage children with a chylothorax.

As evident in Table 4-13, children who developed a chylothorax were most commonly treated with the administration of a medium chain triglyceride (MCT) diet n=154 (89%), and/or the insertion of an intercostal pleural catheter n=150 (86.5%). A smaller number of children were prescribed and administered intravenous (IV) total parenteral nutrition (TPN), n=61 (35.5%), with n =29 (17%) receiving IV OCT/SST.

Table 4-13 Treatment strategies implemented to manage children who developed a chylothorax

Treatment strategy	Number (%)
Medium Chain Triglyceride (MCT) diet*	154 (89)
Insertion of Intercostal Pleural Catheter*	150 (86.5)
Total Parenteral Nutrition (TPN)*	61 (35.5)
Intravenous (IV) Octreotide / Somatostatin*	29 (17)
Thoracentesis*	14 (8)
Low Fat Diet*	13 (7.5)
Intravenous (IV) Immunoglobulin (IVIG)*	11 (6.5)
Ligation of thoracic duct*	5 (3)
Pleurodesis*	4 (2.5)
Steroid therapy*	4 (2.5)

*multiple treatment strategies possible for each child, hence %'s do not =100%

For those children treated with an intercostal pleural catheter, the majority received bilateral insertion n=72 (41.5%), with a right intercostal pleural catheter being the more likely location if a single catheter was used, n=56 (32.5%).

The majority of the children received multiple treatment strategies to manage their chylothorax, with two or three differing treatments being most frequently prescribed and administered. Some children however required five or six

treatments, with one child requiring seven (Table 4-14). Figure 4-3 shows the multiple treatments most commonly administered.

Table 4-14 Number of treatment strategies prescribed and administered to children who developed a chylothorax

Number of treatment strategies prescribed and administered	Number of children receiving each treatment
0	0
1	17
2	87
3	42
4	14
5	7
6	5
7	1
8	0
Total	**173**

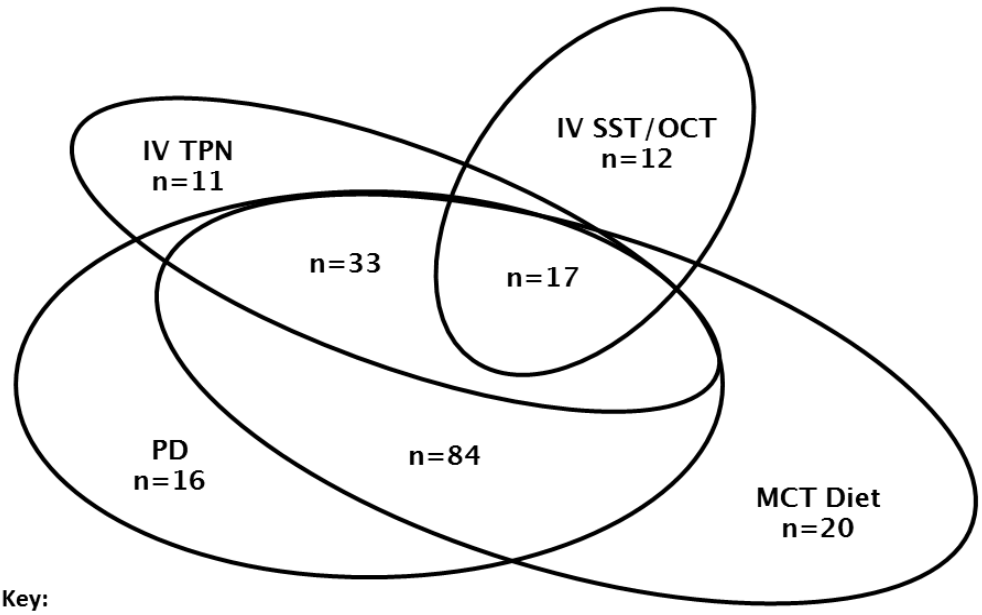


Figure 4-3 The four most commonly administered combined treatments

Findings

The number of reported treatments by primary diagnostic group can be seen in Table 4-15, with children averaging 2.6 treatments (range 2.0-3.4), (median 2). Those children with a neonatal congenital primary diagnosis on average received most treatments, followed by those with a cardiac medical primary diagnosis. It was this latter group who received the maximum number of treatments (seven) for chylothorax management.

Table 4-15 Number of treatments split by primary diagnosis

Primary diagnosis	Number of children	Number of treatments			
		Average	Median	Min.	Max.
Cardiac Surgical	113	2.3	2	1	6
Neonatal Congenital	22	3.4	3	1	6
Surgical (non-cardiac)	14	2.9	3	2	4
Neonatal Other	12	2.8	2	1	5
Cardiac Medical	4	3.3	2.5	1	7
Medical (non-cardiac)	3	2.3	2	2	3
Not Known	3	2.7	2	1	5
Oncology / Haematology	1	3.0	3	3	3
Other	1	2.0	2	2	2
Total	**173**	**2.6**	**2**	**1**	**7**

As identified above, the most frequently administered treatments were the insertion of an intercostal pleural catheter(s), an MCT diet, IV TPN and IV OCT/SST. The number of days these strategies continued for can be seen in Figure 4-4 and Figure 4-5. Further detail is presented in 4.1.12.5, (Table 4-39).

(Box plots showing median and interquartile ranges, whiskers denote range of values, outliers as * or °)

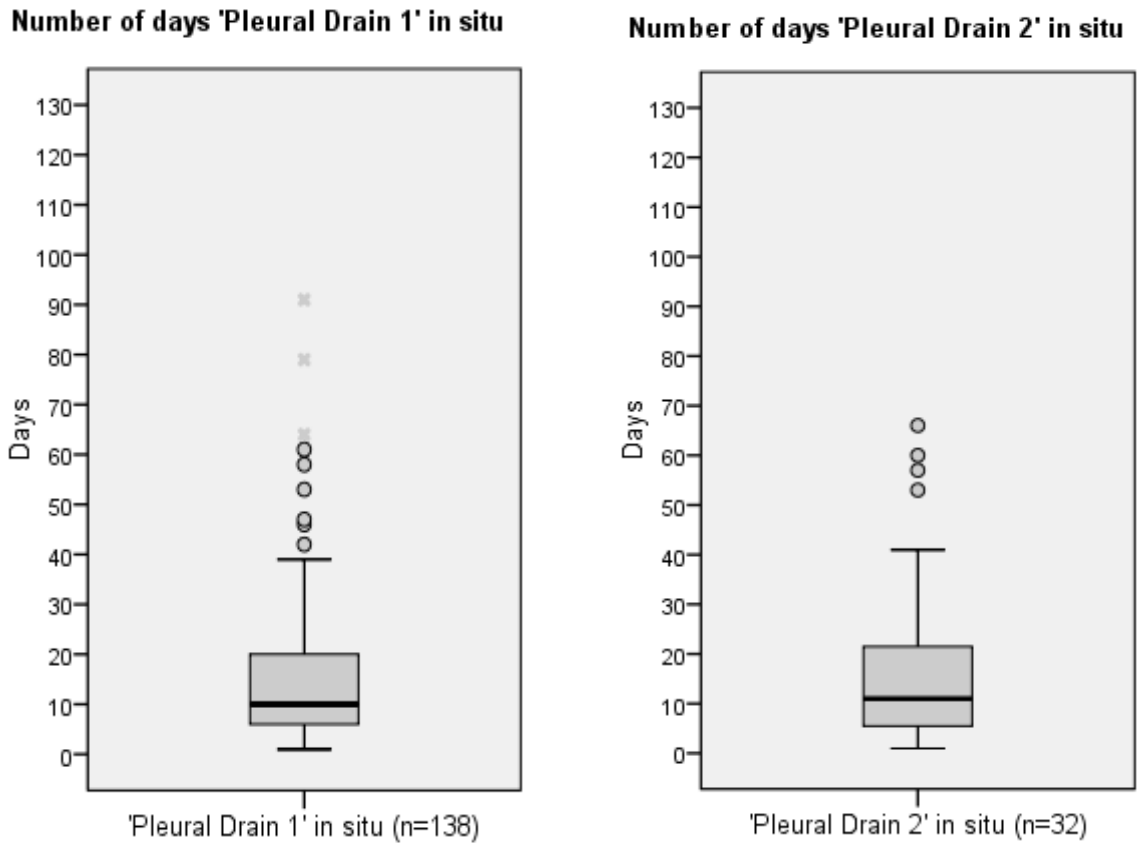


Figure 4-4 Box Plots showing number of days intercostal pleural catheter 1 and intercostal pleural catheter 2 were in situ.

(Box plots showing median and interquartile ranges, whiskers denote range of values, outliers as * or °)

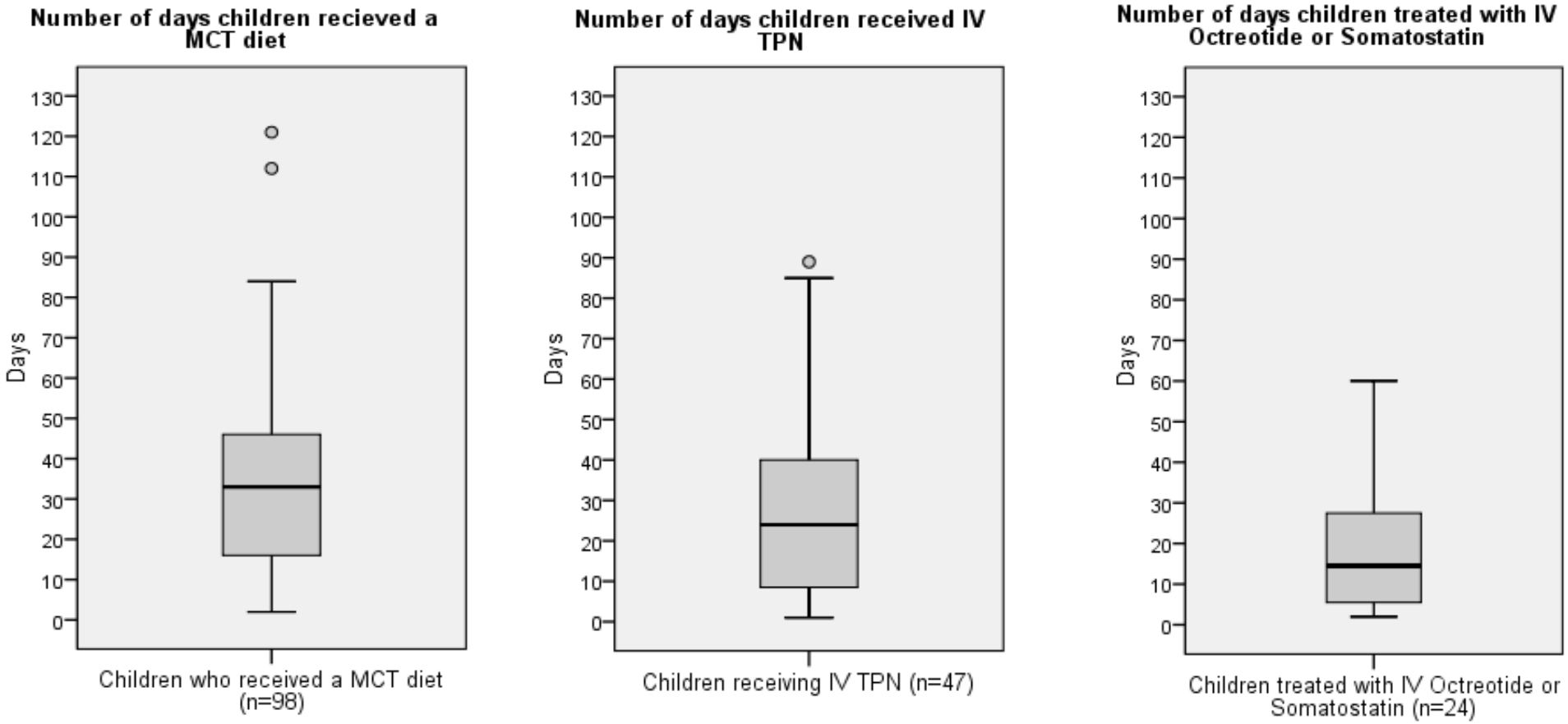


Figure 4-5 Box Plots showing number of days children received MCT diet and/or IV TPN, and or IV OCT or SST

Although the four most frequently administered management strategies have been identified above, a number of children received a combination of treatments in order to aid in their chylothorax management. The most commonly administered were an MCT diet and an intercostal catheter, followed by IV TPN and IV OCT/SST (Figure 4-6), however subsequent treatments varied and included surgical intervention, or administration of intravenous immunoglobulin (IVIG) or steroids.

The Venn diagrams below show the treatment pathways prescribed and administered to the children. Thoracentesis, for respiratory compromise not for primary management, was the most frequently undertaken surgical procedure (n=5) (Figure 4-6), followed by pleurodesis (n=3) (Figure 4-7). Ligation of the thoracic duct was the least frequent procedure and followed treatment with pleurodesis and/or IVIG (Figure 4-8 and Figure 4-9).

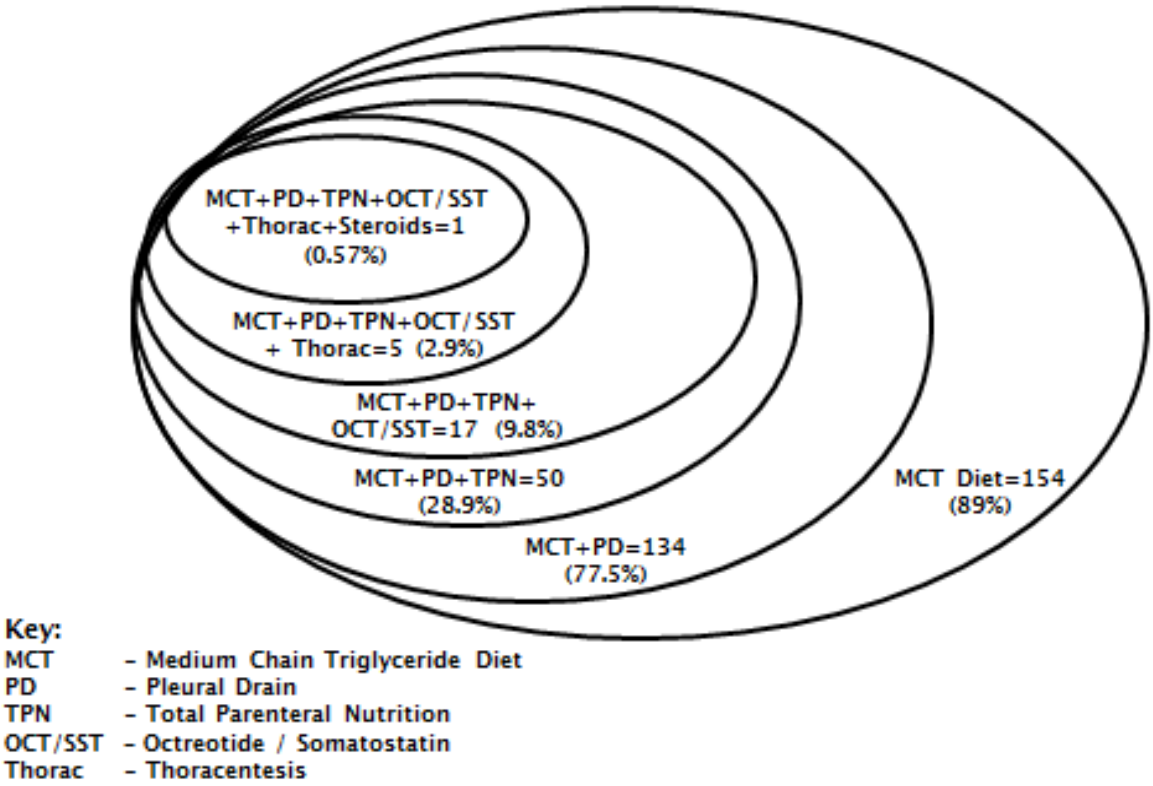


Figure 4-6 Management strategies including thoracentesis and steroids

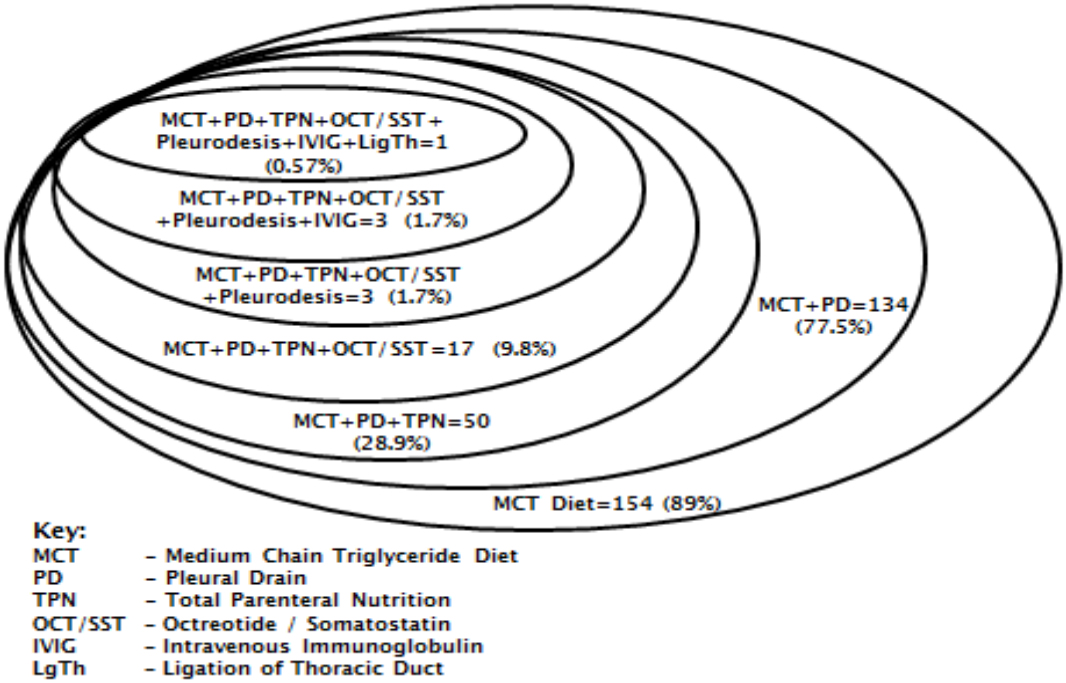


Figure 4-7 Management strategies including pleurodesis, IVIG and ligation of thoracic duct

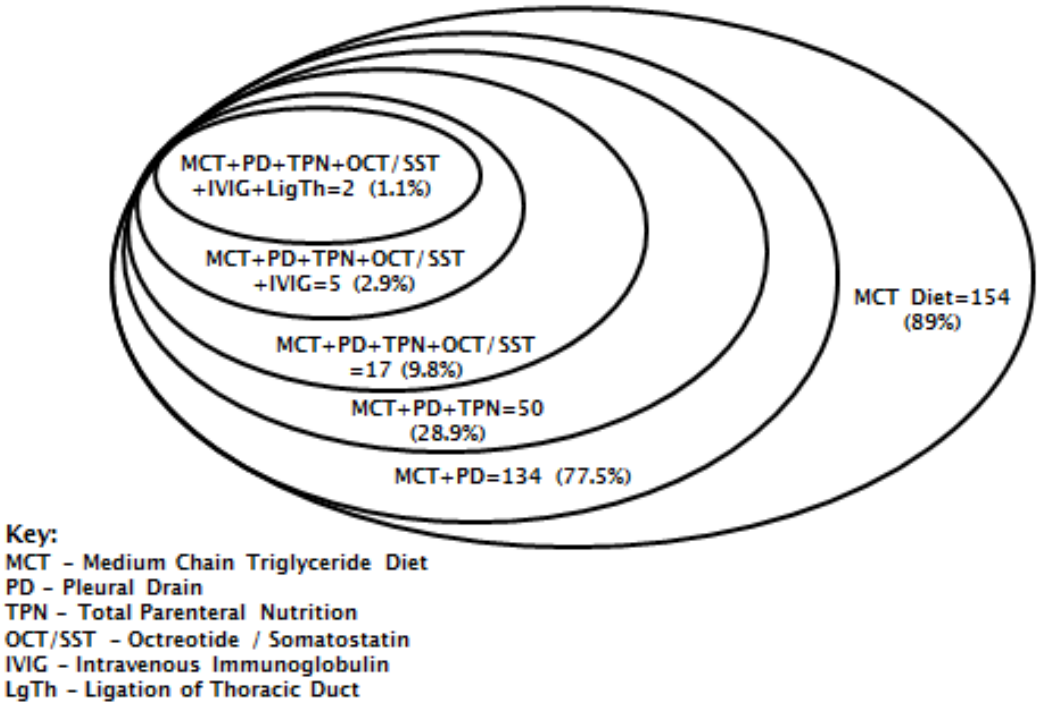


Figure 4-8 Management strategies including IVIG and ligation of thoracic duct

One child who did not receive surgical intervention was prescribed and administered both IVIG and steroids (Figure 4-9).

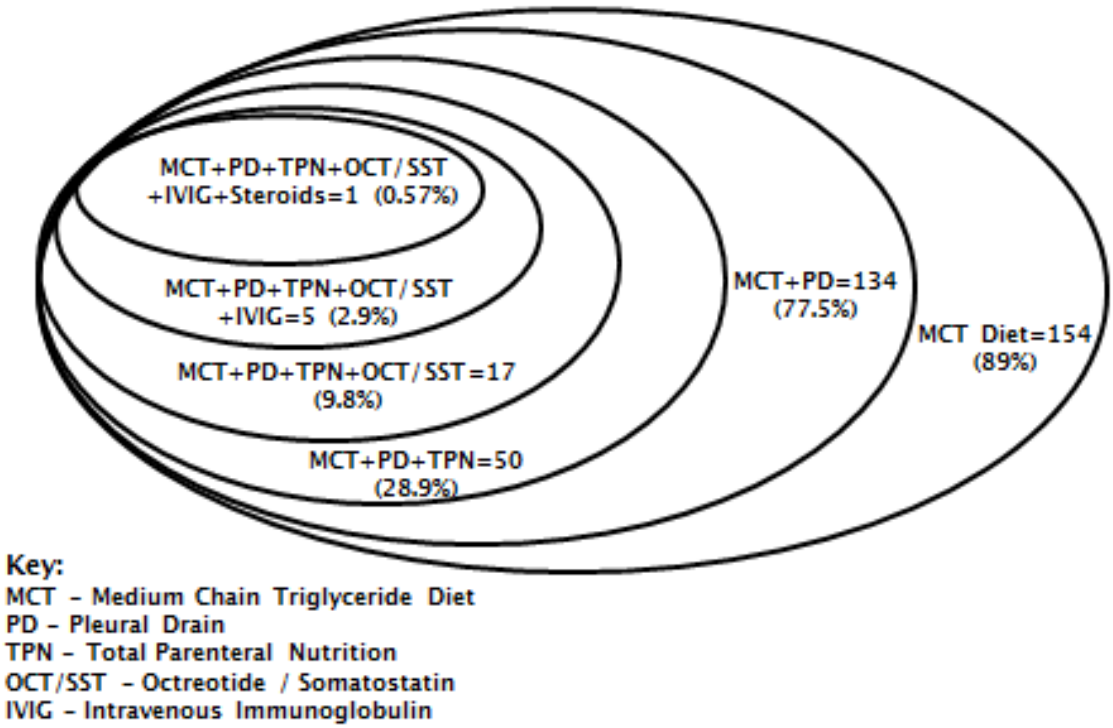


Figure 4-9 Non-surgical management strategies

With no national guidance available for clinicians, the majority of management and treatment strategies followed local physicians' preference (n=121, 69.9%) with a number of centres having a local clinical practice guideline in place (n=75, 43.4%).

In summary, the majority of children were treated with a medium chain triglyceride (MCT) diet, n=154 (89%), followed by the insertion of an intercostal pleural catheter n=150 (86.5%), with most children receiving both these management strategies n=134 (77.5%). IV TPN was the third treatment of choice n=50 (28.9%), with IV OCT/SST being the fourth treatment administered

to n=17 (9.8%) children. Further treatment strategies included surgical intervention and intravenous medications.

4.1.8 Interventional procedure(s) undertaken prior to the chylothorax developing.

Clinicians reported that majority of the children had an interventional procedure undertaken prior to their chylothorax developing (Table 4-16).

Table 4-16 Interventional procedure(s) undertaken prior to the chylothorax developing

Interventional procedure	Number (%)
Intercostal Pleural Catheter Insertion*	118 (68)
Other Surgical Procedure*	116 (67)
Sternotomy*	103 (59.5)
Neck Line Insertion*	78 (45)
Thoracotomy*	31 (18)
Laparotomy*	8 (4.5)

*multiple interventional procedures possible for each child

4.1.9 Length of child's hospital stay and their discharge destination or outcome.

Children remained in hospital for a varying length of time, ranging from 4 to 365 days (median 29.5 days) (IQR 27). However, as can be seen from Figure 4-10, the majority, n=90 (52%) stayed between 11-40 days.

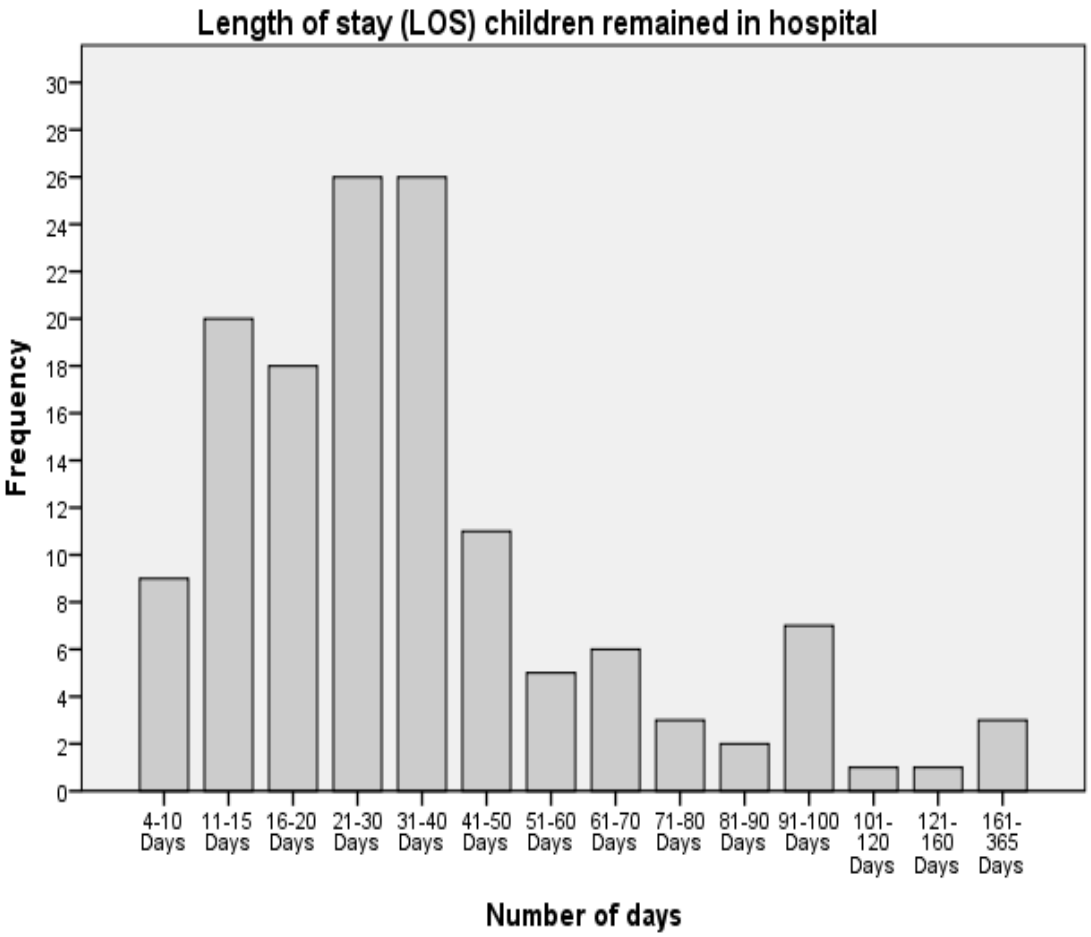


Figure 4-10 Length of stay children remained in hospital

Table 4-17 identifies the children's mean length of stay and their interquartile range (IQR) according to the treatment strategy they received. The majority of children had placement of an intercostal pleural catheter and/or received an MCT diet or IV TPN. These children had a mean length of stay ranging from 40.32-65.80 days, (IQR 30-47). However, if the child received intravenous medication of IV OCT/SST, or IVIG, or required surgical ligation of their thoracic duct, their length of stay was substantially longer, with a mean ranging from 77.11-102 days, (IQR 49-269). At this time determining whether this extended stay was a cause or effect of treatment was not investigated further.

Table 4-17 Treatment strategies administered and the child's related length of hospital stay

Treatment strategy	Treatment administered	Length of Stay (LOS) (days)
		Mean [minimum – maximum] (IQR)
MCT Diet*	n=122**	41.90 [4-365] (31)
Intercostal Pleural Catheter*	n=119**	40.32 [6-365] (30)
IV TPN*	n=44**	65.80 [9-365] (47)
IV OCT/SST*	n=19**	77.11 [12-365] (49)
Thoracentesis*	n=11**	46.36 [23-94] (34)
Low Fat Diet*	n=10**	34.50 [12-66] (40_
IVIG*	n=9**	87.11 [19-365] (53)
Ligation of Thoracic Duct*	n=4**	102 [10-365] (269)
IV Steroids*	n=2**	56.50 [30-83). (n/a)
Pleurodesis*	n=2**	230 [95-365] (n/a)

*multiple treatment strategies possible for each child
**number of children reported reflects the availability for complete LOS data

Although the majority of the children survived their hospital admission and were discharged home, a proportion were still receiving treatment at the time the questionnaire was completed, hence their discharge destination or outcome was unknown (Table 4-18). Of the identified cases n=22 (12.5%) died during the study period.

Table 4-18 Child's hospital discharge destination or outcome

Child's discharge destination or outcome	Number (%) (n=173)
Survived and discharged	117 (67.5)
Treatment continuing	29 (17)
Died	22 (12.5)
Not known	5 (3)

In summary, the hospital length of stay for these children ranged from 4-365 days, with n=52 (35%) staying between 21-40 days. Although some of the children remained in hospital, with treatment continuing when the questionnaire data were submitted, n=117 (67.5%) had been discharged, however n=22 (12.5%) had not survived.

4.1.10 Exploratory Analysis

Six study areas were identified for further analysis, with clinically relevant questions posed within each. Fisher exact test or correlational analyses were applied to five of the study areas depending on the data variables used to answer the question. The last study area applied logistical analysis to establish which clinical variable(s) increase the probability of the child's survival.

1. **The relationship between features of the child and treatment options,** specifically;
    a. Is there any difference in treatment received by children in different weight categories?

Weight at diagnosis rather than age was used to investigate this relationship as it takes account of gestational and developmental variations between children. The interval weight data were transformed into categorical data and the treatment options were collapsed into three distinct categories (Table 4-19). Due to the small number of variables in some data cells Fisher exact test was used to analyse the data.

This test showed that significantly more children in the higher weight category received first line treatment only (p=<0.001) (Table 4-20).

Table 4-19 Interval data and their corresponding categorical variable definitions

Data variable	Category
Child's Weight	• Birth weight = 0-4.99 kgs • Toddler weight = 5.0-9.99 kgs • Child weight = 10.0-29.99 kgs • Adolescent weight = 30.0-54.99 kgs
Child's Primary Diagnosis	• Cardiac (medical and surgical) • Non-cardiac (medical and surgical) • Neonatal • Not known
Treatment Option: 1st line = MCT/low fat diet and or Pleural drain 2nd line = Medical management i.e. TPN, OCT/SST, Steroids, IVIG) 3rd line = Surgical management i.e. thoracentesis, pleurodesis, ligation of thoracic duct	• 1st line treatment • 1st line and 2nd line treatment • 1st line and 2nd line and 3rd line treatment
Hospital Setting	• Tertiary Hospital • District General Hospital (DGH)
Child's Length of Hospital Stay (LOS)	• Short stay = 4-10 days • Medium stay = 11-20 days • Long stay = 21-50 days • Extensive stay = 51-365 days
Child's Outcome	• Survival • Died • Not known

Table 4-20 Number (%) of children receiving each treatment, by weight category.

Weight category (kgs)	**Treatment category frequency (%) n=160**			**Fisher exact test p-value**
	1st line treatment n=89	1st & 2nd line treatment n=53	1st, 2nd & 3rd line treatment n=18	<0.001
Birth weight = 1.00-4.99 kgs n=81	30 (37)	38 (47)	13 (16)	
Toddler Weight = 5.00-9.99 kgs n=47	37 (78.5)	8 (17)	2 (4.5)	
Child Weight =10.00-29.99 kgs n=29	20 (69)	7(24)	2(7)	
Adolescent Weight = 30.00-54.99 kgs n=3	2 (67)	0 (0)	1 (33)	

b. Is there any difference between treatments received by children with different primary diagnoses?

To determine the answer to this question the child's primary diagnostic groups were collapsed into three categories and the treatment options transformed as previously summarised in Table 4-19. Again, Fisher exact test was used to analyse the data.

This test shows a significant difference between diagnostic groups (p=<0.001) with neonates more likely to receive second and third line treatments than those children with a cardiac (medical and surgical) or non-cardiac primary diagnosis (Table 4-21).

Table 4-21 Number (%) of children in each treatment category by primary diagnostic group.

Primary diagnosis	**Treatment category frequency (%) n=160**			**Fisher exact test p-value**
	1st line treatment n=89	1st & 2nd line treatment n=53	1st, 2nd & 3rd line treatment n=18	<0.001
Cardiac (medial & surgical) n=115	75 (65)	32 (28)	8 (7)	
Non-Cardiac n=19	6 (31.5)	12 (63)	1 (5.5)	
Neonatal n=35	12 (34.3)	11(31.5)	12(34.3)	
Not known n=4	1 (25)	2 (50)	1 (25)	

2. **The relationship between features of the child and outcome**, specifically:
    a. Is there any relationship between the child's age and their days of treatment, or length of hospital stay?
    b. Is there any relationship between the child's weight and their days of treatment, or length of hospital stay?

Spearman rho correlation was used to analyse these non-parametric data (Table 4-22). A weak negative correlation was present between the child's weight and length of stay (-0.196, p=0.026) and the child's age at chylothorax diagnosis and length of stay (-0.173, p=0.043), that is, as the child's age and weight increase, their length of stay reduces. Conversely, however there was a weak positive correlation between the child's age and their weight at chylothorax diagnosis and the number of days of treatment (0.207, p=0.033, 0.203, p=0.039), suggesting as the child's age and weight increased, so did the overall number of days treatment they received.

Table 4-22 Relationship between age and weight of the child at chylothorax diagnosis and days of treatment and length of stay.

Spearman rho correlation		Days of treatment	Length of stay (days)
Age at chylothorax diagnosis (months)	Correlation Coefficient p value n	0.207* 0.033 106	-0.173* 0.043 138
Weight at chylothorax diagnosis (kgs)	Correlation Coefficient p value n	0.203* 0.039 104	-0.196* 0.026 128

*Correlation is significant at ≤0.05

c. Is there any difference in survival for children of different weights?

The categorical weight variables and collapsed outcome data categories (Table 4-19) were used to answer this question and Fisher exact test applied. There was no statistical difference (p=0.051) in survival for children in the different weight categories (Table 4-23).

Table 4-23 Number (%) of children surviving, by weight category

Weight category (kgs)	Child survival frequency (%) n=160			Fisher exact test p-value
	Survived n=138	Died n=17	Not known n=5	0.051
Birth weight = 1.00-4.99 kgs n=81	63 (78)	13 (16)	5(6)	
Toddler Weight = 5.00-9.99 kgs n=47	46 (98)	1 (2)	0 (0)	
Child Weight = 10.00-29.99 kgs n=29	26 (90)	3 (10)	0 (0)	
Adolescent Weight = 30.00-54.99 kgs n=3	3 (100)	0 (0)	0 (0)	

d. Is there any difference in length of stay for differing diagnostic groups?

The collapsed primary diagnostic categories and collapsed length of hospital stay categories (Table 4-19) were used to answer this question, with Fisher exact test analysis applied. There was no significant difference (p=0.272) in length of stay between the different primary diagnostic groups (Table 4-24).

Table 4-24 Number (%) of children in each length of stay category, by primary diagnostic group.

Primary diagnosis	**Length of stay (days) frequency (%) n=138**				**Fisher exact test p-value**
	4-10 days n=9	11-20 days n=37	21-50 days n=64	51-365 days n=28	0.272
Cardiac (medial & surgical) n=91	6 (6.5)	30 (33)	40 (44)	15 (16.5)	
Non-Cardiac n=12	1 (8.5)	3 (25)	4 (33.5)	4 (33.5)	
Neonatal n=31	2 (6.5)	3 (9.5)	18 (58)	8 (26)	
Not known n=4	0 (0)	1 (25)	2 (50)	1 (25)	

e. Is there any difference in survival between the different primary diagnostic groups?

The collapsed primary diagnostic and the outcome categories were used to answer this question with Fisher exact test applied. There was no statistically significant difference (p=0.258) in survival outcome between the primary diagnostic categories (Table 4-25).

Table 4-25 Number (%) of children who survived by primary diagnostic category.

Primary diagnosis	**Child survival frequency (%) n=173**			**Fisher exact test p-value**
	Survived n=147	Died n=21	Not known n=5	0.258
Cardiac (medial & surgical) n=115	102 (88.5)	11 (9.5)	2 (2)	
Non-Cardiac n=19	15 (79)	3 (16)	1 (5)	
Neonatal n=35	26 (74)	7 (20)	2 (6)	
Not known n=4	4 (100)	0 (0)	0 (0)	

3. **The relationship between the treatment setting and treatment options,** specifically
    a. Is there any difference between the treatment setting and the treatment options administered?

The hospital categories caring for the child were combined into two categories, either a Tertiary or District General Hospital (DGH) (Table 4-19) and compared by the treatment categories administered. Fisher exact test showed no significant difference (p=0.929) between these categories (Table 4-26).

Table 4-26 Number (%) of children receiving differing treatments by hospital category.

Hospital category	**Treatment category frequency (%) n=173**			**Fisher exact test p-value**
	1st line treatment n=94	1st & 2nd line treatment n=57	1st, 2nd & 3rd line treatment n=22	0.929
Tertiary n=159	86 (54)	53 (33.5)	20 (12.5)	
DGH n=14	8 (57)	4 (28.5)	2 (14.5)	

4. **The relationship between treatment setting and outcome,** specifically,
    a. Is there any difference between the treatment settings in relation to the child's length of stay?

The collapsed hospital categories and the categorised child's length of stay previously summarised in Table 4-19 were used to answer this question and Fisher exact test applied. There was no significant difference (p=0.249) in length of hospital stay between the categories of hospital caring for the child (Table 4-27).

Table 4-27 Number (%) of children in each length of stay category, by hospital category.

Hospital category	**Length of stay (days) frequency (%) n=138**				**Fisher exact test p-value**
	4-10 days n=9	11-20 days n=37	21-50 days n=64	51-365 days n=28	0.249
Tertiary n=125	8 (6)	36 (29)	55 (44)	26 (21)	
District General Hospital (DGH) n=13	1 (7.5)	1 (7.5)	9 (69.5)	2 (15.5)	

b. Is there any difference in survival between the treatment settings?

The combined hospital categories and child's outcome categories previously summarised in Table 4-19 were used to answer this question and Fisher exact test applied. There was no significant difference (p=0.797) in survival between the categories of hospital caring for the child (Table 4-28).

Table 4-28 Number (%) of children surviving, by hospital category.

Hospital category	Child survival frequency (%) n=173			Fisher exact test p-value
	Survived n=147	Died n=21	Not known n=5	0.797
Tertiary n=159	135 (85)	19 (12)	5 (3)	
DGH n=14	12 (85.5)	2 (14.5)	0 (0)	

5. **The relationship between the treatment category and outcome**, specifically,
   a. Is there any difference between the treatments received by the children and their length of hospital stay?

The collapsed treatment categories and the child's length of stay categories previously summarised in Table 4-19 were used to answer this question and Fisher exact test applied. This test shows a significant difference between these groups (p=<0.001) indicating those children who received second and third line treatments, remained in hospital for longer periods of time (Table 4-29).

Table 4-29 Number (%) of children in each treatment category, by length of stay.

Treatment category	**Length of stay (days) frequency (%) n=138**				**Fisher exact test p-value**
	4-10 days n=9	11-20 days n=37	21-50 days n=64	51-365 days n=28	<0.001
1st line treatment n=80	7 (9)	31 (39)	37 (46)	5 (6)	
1st & 2nd line treatment n=42	1 (2.5)	5 (12)	19 (45)	17 (40.5)	
1st, 2nd & 3rd line treatment n=16	1 (6)	1 (6)	8 (50)	6 (38)	

b. Is there any difference in survival for the different treatment categories?

The collapsed treatment categories and the outcome categories previously summarised in Table 4-19 were used to answer this question and Fisher exact test applied. This test shows a significant difference between these groups (p=<0.001) indicating children solely receiving first line treatment were more likely to survive (Table 4-30).

Table 4-30 Number (%) of children in each treatment category, by survival.

Treatment category	Child outcome frequency (%) n=173			Fisher exact test p-value
	Survived n=147	Died n=21	Not known n=5	<0.001
1st line treatment n=94	90 (95.5)	4(4.5)	0 (0)	
1st & 2nd line treatment n=57	44 (77)	10 (17.5)	3 (5.5)	
1st, 2nd & 3rd line treatment n=22	13 (59)	7 (32)	2 (9)	

6. **The probability of the child's survival.**

a. Which clinical variables influenced the probability of the child's survival?

The child's survival outcome was focused on within this question due to its clinical relevance and importance. The interval data of weight and age and the categorical data of gender, hospital category, primary diagnosis, treatment group and length of stay (Table 4-19) were used to answer this question with binary logistical analysis applied (Table 4-31). There was no statistical significance in the probability of whether the child survived or not in relation to the category of hospital caring for them (p=0.799), the category of their length of hospital stay when compared to the reference group (p=0.959, p=0.348, p=0.712), or their primary diagnosis when compared to the reference group (p=0.894, p=902) (Table 4-31).

Table 4-31 Probability of child's survival compared to specific clinical variables.

Clinical Variable	Regression Parameter (B)	Standard Error (SE)	p-value
	(n=124)		
Age at chylothorax diagnosis (mths)	0.072	0.029	0.012
Weight (kgs)	-0.371	0.137	0.007
Gender (reference group –female)	-1.614	0.758	0.033
Hospital category (reference group – DGH)	-0.343	1.347	0.799
Primary diagnostic group – Neonatal (reference group)	-	-	0.989
Primary diagnostic group – Cardiac	0.113	0.847	0.894
Primary diagnostic group – Non-Cardiac	0.184	1.499	0.902
Length of stay -4-10 days (reference group)	-	-	0.508
Length of stay – 11-20 days	-0.077	1.447	0.959
Length of stay – 21-50 days	-1.392	1.482	0.348
Length of stay – 51-365 days	-0.551	1.490	0.712
Treatment category – 1st Line (reference group)	-	-	0.003
Treatment category – 2nd Line	2.177	0.914	0.017
Treatment category – 3rd Line	4.083	1.219	0.001

However, there were some clinical variables that were strongly associated with the child's survival or non-survival. There was an increased probability of children being in the non-survival group as their age increased (p=0.012), although as the child's weight increased there was a greater probability of them being in the survival group (p=0.007). Boys had a greater probability of being in the survival group (p=0.033) and when compared to the reference group, those children who received second and third line treatments had an increased probability of being in the non-survival group (p=0.017, p=0.001) (Table 4-31).

4.1.11 Free text data analysis

Section 8 of the questionnaire provided the opportunity for clinicians to document any additional information they felt to be of importance to the case. 67% (n=116) of respondents provided additional information and this was classified into the following four themes:

- Complex Cases
- Treatment Clarification
- Child's follow-up
- Missing Data

The majority of qualitative data related to clinicians explaining the diagnosis and multiple management strategies prescribed to treat the more complex children who developed a chylothorax. They provided detailed information on the child's underlying condition, the treatment therapies implemented, additional medications and the surgical procedures required. Where the child died further detailed information was provided.

Those clinicians offering additional information on treatment options focused on two areas. Firstly the length of time for which an MCT diet was prescribed and administered and secondly the decision-making process regarding the chosen treatment pathway.

A number of clinicians commented that the child has been transferred to their local DGH, hence further follow-up information would need to be obtained from this location. Those clinicians commenting on 'missing data', wanted to apologise and clarify that certain documents or results were unavailable at the time the questionnaire was completed.

4.1.12 Sub-analysis of children who developed a chylothorax following cardiac surgery, n=113 (65.3%)

In view of the large proportion of the population whose chylothorax developed following cardiac surgery, a sub group analysis of these children was undertaken. The results of this analysis are presented in the following section.

4.1.12.1 Demographic characteristics of the children having cardiac surgery.

In contrast to the total study population (Section 4.1.2), within this sub-group fewer boys than girls developed a chylothorax, however similarly, the majority n=89 (78.5%) were from a white ethnic background, with all ethnicities being represented (Table 4-32).

Table 4-32 Gender and ethnicity of children who developed a chylothorax following cardiac surgery

Demographic characteristic		Number (%) n=113
Gender:	Male	53 (47)
Ethnicity:	White	89 (78.5)
	Asian or Asian British	16 (14)
	Black or Black British	4 (3.5)
	Mixed	2 (2)
	Other	2 (2)

The gestational age and birth weight of these children reflected the group as a whole (Table 4-33).

Table 4-33 Clinical features of children who developed a chylothorax following cardiac surgery

Clinical feature	Median (range) [IQR}	Mean [95% CI for mean]
Birth Weight if ≤1 yr (kgs)	2.8 (0.78 – 4.40) [0.93]	2.77 [2.57-2.97]
Weight at diagnosis (kgs)	5.7 (1.50 – 51.40) [5.82]	7.89 [6.66-9.12]
Gestational age if ≤1 yr (wks) at presentation of chylothorax	38.8 (28 – 41.57) [3]	38 [37.3-38.7]
Age at diagnosis (months)	6 (0 – 168) [22]	19.5 [14.10-24.99]

Of particular note were the number of children within this sub-group that had a congenital disorder n=24 (21.2%), with Down syndrome being the most frequently reported n=16 (14.1%) (Table 4-34). Of the children who developed a chylothorax and were reported as having a congenital disorder, n=24 (80%) had required cardiac surgery (Table 4-3).

Table 4-34 Congenital disorders of children who developed a chylothorax following cardiac surgery

Congenital disorder	Number (%) (n=113)
Down syndrome	16 (14.1)
Noonan syndrome	3 (2.6)
DiGeorge syndrome	2 (1.7)
Apert syndrome	2 (1.7)
Turner syndrome	1 (0.9)
Total	**24 (21.2)**

4.1.12.2 Diagnosis of the child's chylothorax.

Predictably, the most common method for confirming the development of the chylothorax was by laboratory analysis of pleural, n=77 (68%). The underlying clinical diagnosis of the child, n=38 (33.5%), the timing of the development of the chylothorax, n=30 (26.5%) and the speed of the chylothorax accumulation n-23 (20.5%), were also reported as diagnostic strategies (Table 4-35).

Table 4-35 Method(s) used to diagnose the chylothorax in children who developed the effusion following cardiac surgery

Diagnostic category	Diagnosis of a chylothorax Number (%)
Laboratory confirmation - triglyceride content of pleural fluid >1.1 mmol / litre*	77 (68)
Underlying clinical diagnosis of the child*	38 (33.5)
Timing of the development of the chylothorax*	30 (26.5)
Speed of accumulation of the chylothorax*	23 (20.5)
Pleural drainage was cloudy by no laboratory confirmation sought*	19 (17)
Laboratory confirmation - total cell count of pleural fluid ≥1000 cells / microliter*	15 (13.5)
Laboratory confirmation - lymphocyte predominance in pleural fluid ≥80%*	14 (12.5)
Pleural effusion on x-ray or ultrasound - No Pleural drain inserted*	11 (10)
Clinical suspicion of chylothorax - No pleural drain inserted*	8 (7)

* n=113 (100%) possible for each diagnostic category

4.1.12.3 Risk Adjustment for Congenital Heart Surgery (RACHS-1) Categories.

Within the questionnaire, clinicians provided free text information on the primary diagnosis of the child and in an attempt to gain a greater understanding of the link chylothorax has with cardiac surgery, the diagnostic

categories of these children were further classified according to the RACHS-1 (Risk Adjustment for Congenital Heart Surgery) categories. This system stratifies the anatomic diversity of the cardiac condition into six groupings based on the child's age and type of surgery performed, with the aim of increasing predicted operative risk (Jenkins *et al.* 2002) (Appendix 7). Category 1 is low risk, with Category 6 having the highest risk.

The detail of the information provided by clinicians varied, with some being complex and in-depth, whilst others were concise and limited. On the information provided the children were categorised into one of the six RACHS-1 categories (Table 4-36). The results show a distribution across five of the six categories, with RACHS-1 Category 3 being the most common n=52 (46%), followed by RACHS-1 Categories 2 n=40 (35.3%). These two categories accounted for 81.3% of all children who required cardiac surgery. There were fewer children in Categories 1, 4 and 6, n=4-11 (3.5-9.7%). No comparative data for any country in the UK were available.

Table 4-36 RACHS-1 Category of children who developed a chylothorax following cardiac surgery

RACHS-1 Category	Number (%) (n=113)
Risk Category 1	6 (5.3)
Risk Category 2	40 (35.3)
Risk Category 3	52 (46)
Risk Category 4	11 (9.7)
Risk Category 5	0 (0)
Risk Category 6	4 (3.5)

The highest proportion of children in RACHS-1 Category 3 had an underlying condition requiring a Fontan procedure (n=21, 40%), with those children who had Down syndrome in combination with an atrio-ventricular septal defect being the second most reported group (n=10, 19%). Children in RACHS-1

Category 2 most commonly requiring surgery for Tetralogy of Fallot n=15 (37.5%).

4.1.12.4 Hospitals caring for children requiring cardiac surgery.

Fourteen hospitals reported caring for cardiac surgical children who developed a chylothorax within the study period. With the UK centralisation of paediatric cardiac surgery facilities, it was surprising to find three non-tertiary cardiac centres (a District General Hospital (DGH) and two Tertiary Combined Hospitals) had reported caring for children who had developed a chylothorax following cardiac surgery. On closer analysis however the former was a child who had developed a chylothorax following a patent ductus arteriosus (PDA) repair. This may have been an interventional rather than operative procedure and therefore possibly undertaken in this neonatal unit, although this would not be normal practice in a DGH. Conversely, the children reported from the two Tertiary Combined Hospitals had been transferred to these centres for on-going care following cardiac surgery undertaken in a tertiary cardiac centre, which had not reported either case.

Each of the fourteen reporting hospitals were categorised, as previously described in Section 4.1.6, and mapped to their corresponding Strategic Health Authority (SHA). The results are presented in Table 4-37 which again shows that these children are cared for in hospitals based in SHAs across the UK.

Table 4-37 Category of hospital caring for children who developed chylothorax following cardiac surgery and their corresponding Strategic Health Authority

Strategic Health Authority	Category of the hospital caring for the children Number (%)			
	Tertiary Cardiac	Tertiary Neonatal	District General Hospital	Total
SHA 1	4 (3.5)	0 (0)	0 (0)	**4 (3.5)**
SHA 2	11 (9.7)	0 (0)	0 (0)	**11 (9.7)**
SHA 3	22 (19.5)	2 (1.8)	1 (0.9)	**25 (22.2)**
SHA 4	6 (5.3)	0 (0)	0 (0)	**6 (5.3)**
SHA 5	19 (16.8)	0 (0)	0 (0)	**19 (16.8)**
SHA 6	4 (3.5)	1 (0.9)	0 (0)	**5 (4.4)**
SHA 7	8 (7.1)	0 (0)	0 (0)	**8 (7.1)**
SHA 8	8 (7.1)	0 (0)	0 (0)	**8 (7.1)**
SHA 9	1 (0.9)	0 (0)	0 (0)	**1 (0.9)**
SHA 10	12 (10.6)	0 (0)	0 (0)	**12 (10.6)**
SHA 12	14 (11.5)	0 (0)	0 (0)	**14 (12.4)**
Total	**109 (9.4)**	**3 (2.7)**	**1 (0.9)**	**113 (100)**

4.1.12.5 Treatment strategies prescribed and administered to children who developed a chylothorax following cardiac surgery

Treatment strategies for this sub-group reflected those of the entire group with the insertion of an intercostal pleural catheter n=98 (86.5%) and MCT diet n=105 (93%) being the most common (Table 4-38), with IV TPN, n=27 (24%) and IV OCT/SST n=13 (11.5%) also being administered more frequently than other remaining strategies. No child in this sub-group was administered intravenous steroids.

Table 4-38 Treatment strategies prescribed and administered to those children who developed a chylothorax following cardiac surgery

Treatment strategy*	Number (%) (n=113 for each treatment)
Medium Chain Triglyceride (MCT) diet*	105 (93)
Insertion of Intercostal Pleural Catheter*	98 (86.5)
Total Parenteral Nutrition (TPN)*	27 (24)
Intravenous (IV) Octreotide / Somatostatin*	13 (11.5)
Low Fat Diet*	7 (6.2)
Intravenous (IV) Immunoglobulin (IVIG)*	7 (6)
Ligation of thoracic duct*	3 (2.5)
Thoracentesis*	2 (1.8)
Pleurodesis*	2 (1.8)
Steroid therapy*	0 (0)
Other*	5 (4.5)

*multiple treatment strategies possible for each child

For those children treated with an intercostal pleural catheter, most required bilateral insertion n=45 (39.8%), with a right intercostal pleural catheter again being the more likely location if a single catheter was required, n=37 (32.7%).

Insertion of an intercostal pleural catheter, a MCT diet, IV TPN and IV OCT/SST were the four most frequently prescribed and administered treatments. The number of days these treatments extended for can be seen below in Figure

4-11 and Figure 4-12. The mean number of days, 95% CI and the interquartile range for both intercostal pleural catheters remaining in situ and the length of time IV TPN was prescribed and administered were similar to the non-cardiac surgical group (Table 4-39). Although the median number of days this cardiac sub-group of children received an MCT diet (n=37) was longer than the remaining non-cardiac surgical group (n=17), the mean number of days were more comparable (35.61 vs. 29 days). Cardiac surgical children received IV OCT or SST for a significantly shorter period of time than other children in the group with a mean of 9.55 days vs. 26 days (Table 4-39).

(Box plots showing median and interquartile ranges, whiskers denote range of values, outliers as * or ◦). Case numbers differ from Table 4-38 due to data not submitted or missing.

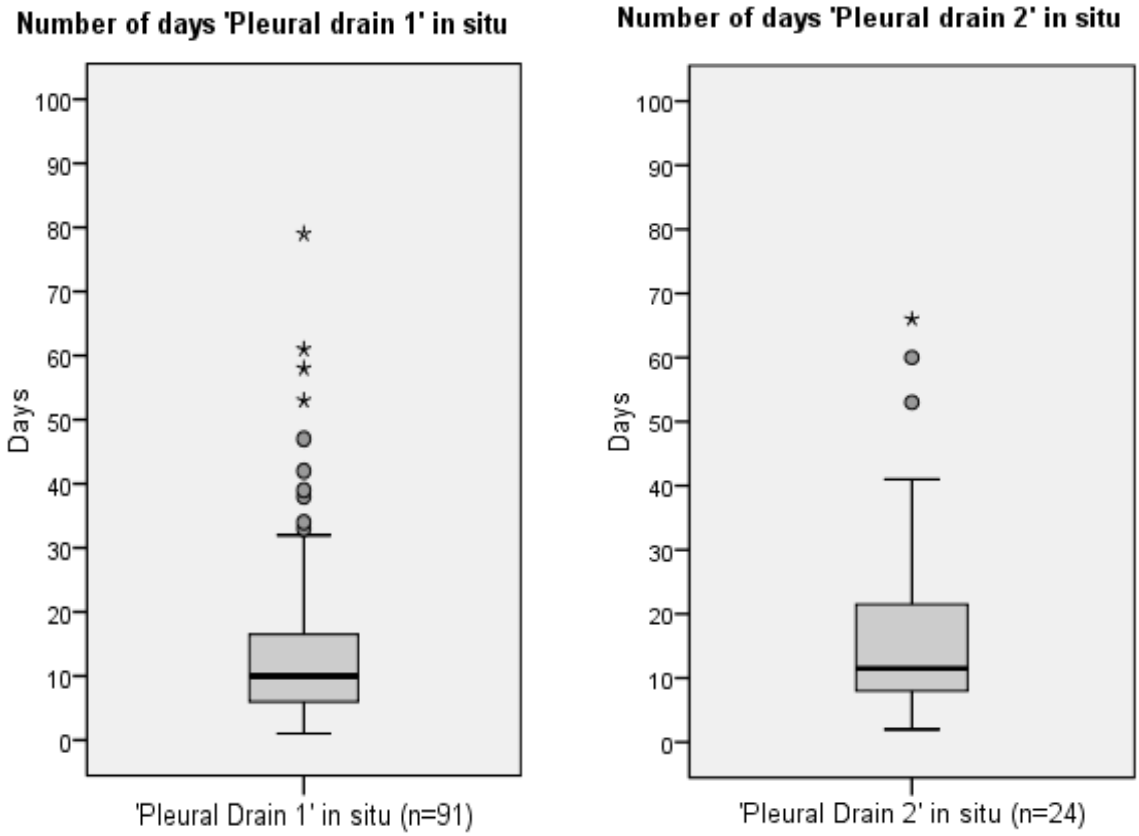


Figure 4-11 Box Plots showing number of days intercostal pleural catheter 1 and intercostal pleural catheter 2 were in situ.

(Box plots showing median and interquartile ranges, whiskers denote range of values, outliers as * or °). Case numbers differ from Table 4-38 due to data not submitted or missing

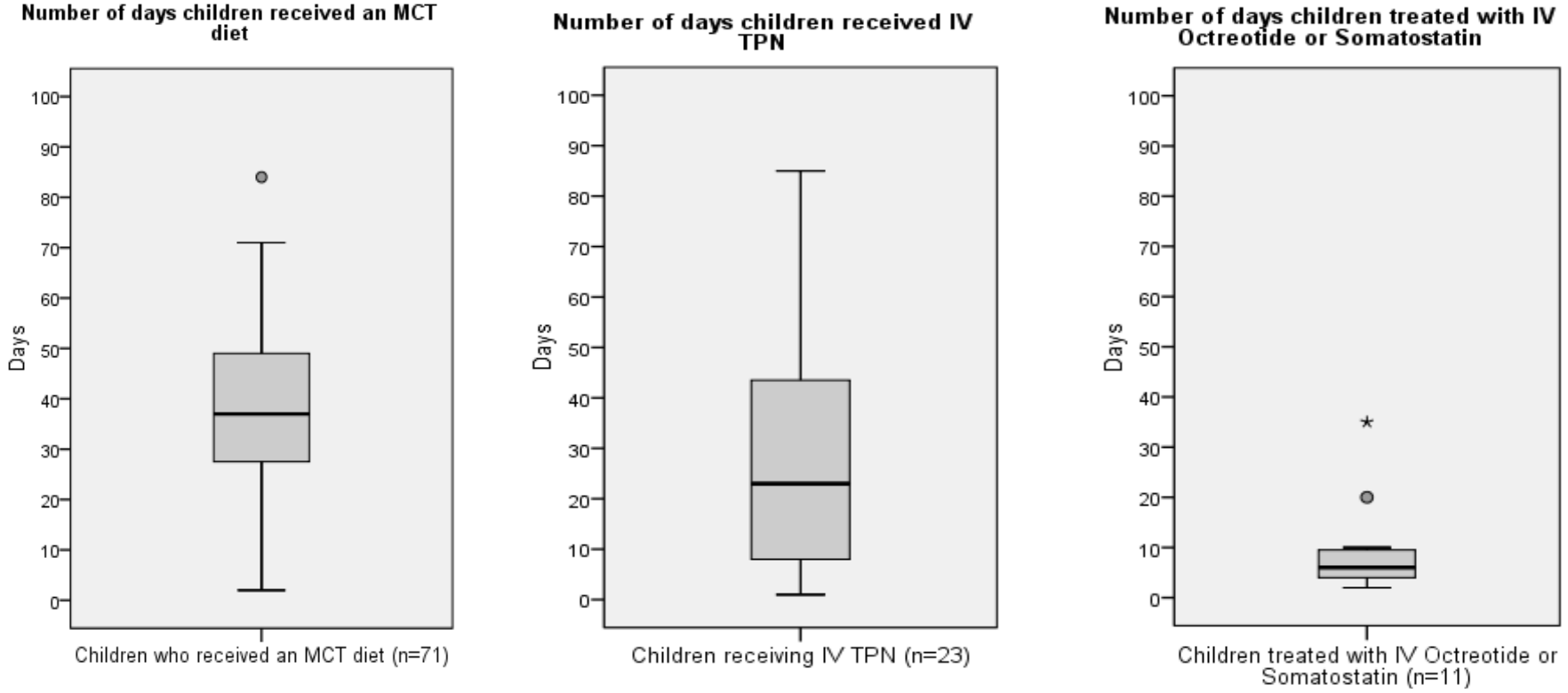


Figure 4-12 Box Plots showing number of days cardiac surgical children received MCT diet and/or IV TPN, and or IV OCT or SST

Table 4-39 Number of days of the four primary treatment strategies. Comparison between children who did and those who did not have cardiac surgery

Treatment strategy	Days of treatment	
	Cardiac surgical sub-group population	Non cardiac surgical population
	Median (Range) [IQR] Mean [95%CI for mean]	
Intercostal Pleural Catheter – Drain 1	10 (1-79) [11] 15.8 [11.99-18.17] (n=91)*	12 (4-91) [15] 17.49 [12.57-22.40] (n=47)
Intercostal Pleural Catheter – Drain 2	11.5 (2-66) [15] 18.67 [11.01-26.32] (n=24)*	8 (1-57) [30] 17.50 [.65-34-35] (n=8)
Medium Chain Triglyceride (MCT) diet	37 (2-84) [23] 35.61 [31.40-39.81] (n=71)*	17 (2-121) [32] 29 [16.40-41.60] (n=27)
Total Parenteral Nutrition (TPN)	23 (1-85) [39] 28.13 [18.19-38.07] (n=23)*	25 (6-89) [27] 28.79 [20.03-37.55] (n=24)
Intravenous (IV) Octreotide / Somatostatin	6 (2-35) [6] 9.55 [2.97-16.12] (n=11)*	21 (4-60) [25] 26 [16.43-35.57] (n=13)

*the number of days of treatment for each management strategy were not always provided by clinicians, therefore total numbers vary to Figure 4-13.

Additional management strategies to the above four most frequently prescribed and administered treatments were more limited within this sub-group of children, in comparison to those seen in the entire group. Surgical intervention remained uncommon, with pleurodesis being the most frequent treatment administered n=2 (1.7%) (Figure 4-13). Only one child received ligation of their thoracic duct, following management with the above four strategies and no child received a thoracentesis. IVIG was prescribed and administered to n=3 (2.6%) children (Figure 4-13), with no child within this sub-group receiving steroids.

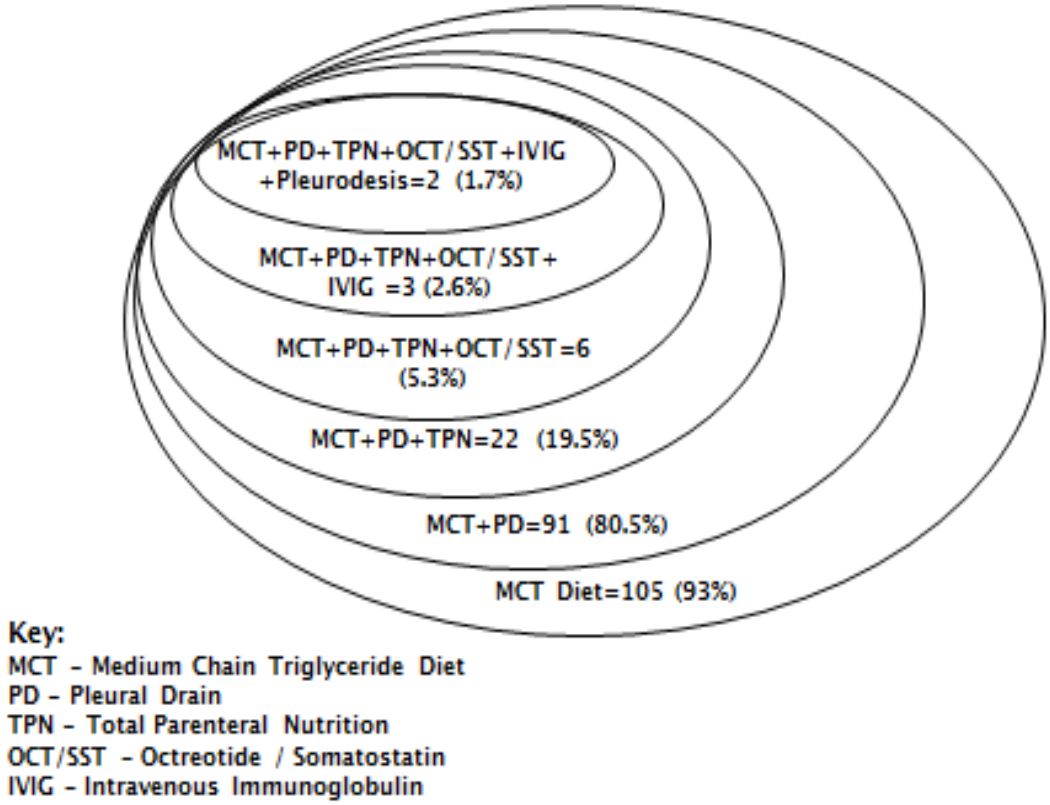


Figure 4-13 Medical and surgical management strategies

4.1.12.6 Interventional procedure(s) undertaken prior to the chylothorax developing.

By definition, all children who required cardiac surgery had been exposed to interventional procedures prior to their chylothorax developing (Table 4-40). Surgical access via a sternotomy or thoracotomy would have been necessary, as well as central intravenous access to aid drug therapy delivery and intercostal pleural catheter(s) inserted to prevent fluid accumulation.

Table 4-40 Interventional procedures undertaken prior to the child developing a chylothorax

Interventional procedure	Number (%)
Intercostal Pleural Catheter Insertion*	98 (86.5)
Sternotomy*	96 (85)
Neck Line Insertion*	69 (61)
Thoracotomy*	17 (15)
Laparotomy	4 (3.5)
None	0 (0)

*multiple interventional procedures possible for each child

4.1.12.7 Length of child's hospital stay and their discharge outcome

As with the BPSU population, this group of children remained in hospital for varying lengths of time, ranging from 6 to 227 days (median 24 days) (IQR 24), with the majority n=65 (57.5%) staying between 11 – 40 days, (Figure 4-14), which corresponded to the entire group.

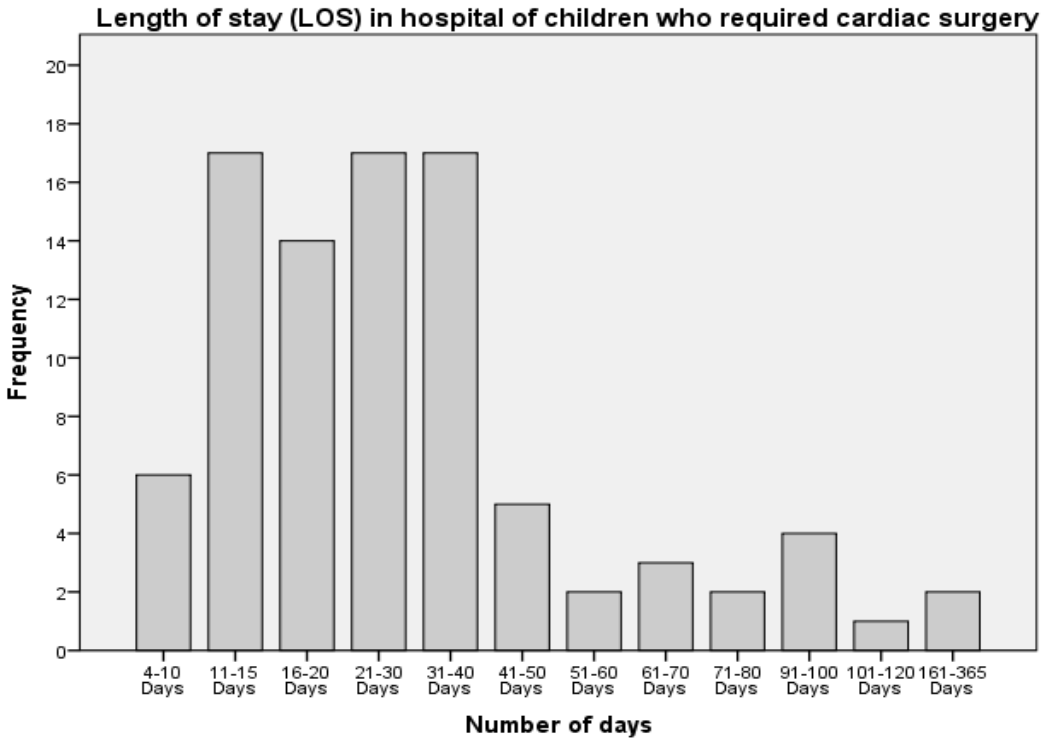


Figure 4-14 Length of hospital stay of children who required cardiac surgery

Findings

Table 4-41 shows the children's mean length of stay according to the treatment strategy they received. The majority of children received an MCT diet or had placement of an intercostal pleural catheter. These treatment strategies had a mean length of stay ranging from 34.23 – 36.17 days. However, if the child received intravenous IV TPN, IV OCT or SST, or IVIG, their length of stay was substantially longer, with a mean ranging from 45.40 – 71.05 days.

Table 4-41 Treatment strategies prescribed and administered to children who developed a chylothorax following cardiac surgery and their associated length of hospital stay

Treatment Strategy	Treatment administered	Length of Stay (LOS) (days)
		Mean [minimum-maximum]
MCT Diet	n=84	36.17 [6-227]
Intercostal Pleural Catheter	n=77	34.23 [6-221]
IV TPN	n=19	71.05 [12-227]
IV OCT/SST	n=9	47.67 [12-95]
IVIG	n=5	45.40 [19-95]
Low Fat Diet	n=4	45.25 [20-66]
Ligation of Thoracic Duct	n=2	16.50 [12-21]
Pleurodesis	n=1	n/a
Thoracentesis	n=1	n/a
IV Steroids	n=0	0

Most children were discharged home, however some were still receiving treatment at the time the questionnaire was completed, hence their discharge destination or outcome was unknown (Table 4-42). This sub-group identified a slightly lower mortality rate than the entire group of children n=11 (9.5%) (Table 4-18).

Table 4-42 Discharge destination or outcome of children, comparing cardiac surgical vs non-cardiac surgical children

Child's discharge destination or outcome	Children who had cardiac surgery Number (%) (n=113)	Children who did not have cardiac surgery Number (%) (n=60)
Survived and discharged	82 (72.5)	35 (58.3)
Treatment continuing	18 (16)	11 (18.3)
Died	11 (9.5)	11 (18.3)
Not known	2 (2)	3 (5)

4.1.12.8 Exploratory Analysis – Cardiac Surgical Children

A repeat of the exploratory analysis undertaken in Section 4.1.10 was applied to this cardiac surgical sub-group data, to identify whether any additional differences or relationship existed between any of the categories.

1. **The relationship between features of the child and treatment options,** specifically;
    a. Is there any difference in treatment received by children in different weight categories?

This analysis showed that significantly more children in the middle weight categories received solely first line treatment (p=<0.008) (Table 4-43).

Table 4-43 Children requiring cardiac surgery - Number (%) of children receiving each treatment, by treatment category.

Weight category (kgs)	**Treatment category frequency (%) n=111**			**Fisher exact test p-value**
	1st line treatment n=72	1st & 2nd line treatment n=32	1st, 2nd & 3rd line treatment n=7	<0.008
Birth weight = 1.00-4.99 kgs n=44	22 (50)	19 (43)	3 (7)	
Toddler Weight = 5.00-9.99 kgs n=41	33 (80.5)	7 (17)	1 (2.5)	
Child Weight =10.00-29.99 kgs n=25	17 (68)	6 (24)	2 (8)	
Adolescent Weight = 30.00-54.99 kgs n=1	0 (0)	0 (0)	1 (100)	

2. **The relationship between features of the child and outcomes**, specifically:
    a. Is there any relationship between the child's age and their days of treatment or length of hospital stay?
    b. Is there any relationship between the child's weight and their days of treatment or length of hospital stay?

Spearman rho correlation showed no strong positive or negative association(s) between any one of the variables. However, a weak positive correlation was present between the age of the child at diagnosis of the chylothorax and the days of treatment (0.264, p=0.023) suggesting as the child's age increased, so did the overall number of days of treatment (Table 4-44).

Table 4-44 Children requiring cardiac surgery – Relationship between age and weight of the child at chylothorax diagnosis and days of treatment and length of stay.

Spearman rho correlation		Days of treatment	Length of stay (days)
Age at chylothorax diagnosis (months)	Correlation Coefficient p value n	0.264* 0.023 74	-0.040 0.710 90
Weight at chylothorax diagnosis (kgs)	Correlation Coefficient p value n	0.221 0.059 74	-0.090 0.400 90

*Correlation is significant at ≤0.05

    c. Is there any difference in survival for children of different weights?

For those children developing a chylothorax following cardiac surgery, there was no significant difference (p=0.136) in survival for children in the different weight categories (Table 4-45).

Table 4-45 Children requiring cardiac surgery – Number (%) of children surviving, by weight category.

Weight category (kgs)	Child survival frequency (%) n=111			Fisher exact test p-value
	Survived n=98	Died n=11	Not known n=2	0.136
Birth weight = 1.00-4.99 kgs n=44	35 (79.5)	7 (16)	2 (4.5)	
Toddler Weight = 5.00-9.99 kgs n=41	40 (97.5)	1 (12.5)	0 (0)	
Child Weight = 10.00-29.99 kgs n=25	22 (88)	3 (12)	0 (0)	
Adolescent Weight = 30.00-54.99 kgs n=1	1 (100)	0 (0)	0 (0)	

3. **The relationship between the treatment setting and treatment options,** specifically
    a. Is there any difference between the treatment setting and the treatment options administered?

Fisher exact test showed no significant difference (p=0.354) between these categories (Table 4-46).

Table 4-46 Children requiring cardiac surgery – Number (%) of children receiving differing treatments by hospital category.

Hospital category	Treatment category frequency (%) n=113			Fisher exact test p-value
	1st line treatment n=73	1st & 2nd line treatment n=33	1st, 2nd & 3rd line treatment n=7	0.354
Tertiary n=112	73 (65.5)	32 (28.5)	7 (6)	
DGH n=1	0 (0)	1 (100)	0 (1)	

4. **The relationship between treatment setting and outcome,** specifically,
    a. Is there any difference between the treatment settings in relation to the child's length of stay?

There was no significant difference (p=1.000) in length of hospital stay between the categories of hospital caring for the child (Table 4-47).

Table 4-47 Children requiring cardiac surgery – Number (%) of children receiving differing treatment, by hospital category.

Hospital category	Length of stay (days) frequency (%) n=90				Fisher exact test p-value
	4-10 days n=6	11-20 days n=30	21-50 days n=40	51-365 days n=14	1.000
Tertiary n=89	6 (7.5)	30 (33.5)	39 (43.5)	14 (15.5)	
DGH n=1	0 (0)	0 (0)	1 (100)	0 (0)	

    b. Is there any difference in survival between the treatment settings?

There was no significant difference (p=0.115) in survival between the categories of hospital caring for the child (Table 4-48).

Table 4-48 Children requiring cardiac surgery – Number (%) of children surviving, by hospital category.

Hospital category	Child survival frequency (%) n=113			Fisher exact test p-value
	Survived n=100	Died n=11	Not known n=2	0.115
Tertiary n=112	100 (88)	10 (9)	2 (2)	
DGH n=1	0 (0)	1 (100)	0 (0)	

5. **The relationship between the treatment category and outcome**, specifically,
    a. Is there any difference between the treatments received by the children and their length of hospital stay?

Fisher exact test showed a significant difference between these groups (p=<0.005) indicating those children who developed a chylothorax following cardiac surgery and received second and or third line treatments, remained in hospital for longer periods of time (Table 4-49).

Table 4-49 Children requiring cardiac surgery – Number (%) of children in each treatment category, by length of stay.

Treatment category	**Length of stay (days) frequency (%) n=90**				**Fisher exact test p-value**
	4-10 days n=6	11-20 days n=30	21-50 days n=40	51-365 days n=14	<0.005
1st line treatment n=61	6 (10)	25 (41)	26 (42.5)	4 (6.5)	
1st & 2nd line treatment n=25	0 (0)	4 (16)	12 (48)	9 (36)	
1st, 2nd & 3rd line treatment n=4	0 (0)	1 (25)	2 (50)	1 (25)	

b. Is there any difference in survival for the different treatment categories?

Fisher exact test showed a significant difference between these groups (p=<0.001) indicating those children who developed a chylothorax following cardiac surgery and who solely received first line treatment were more likely to survive (Table 4-50).

Table 4-50 Children requiring cardiac surgery – Number (%) of children in each treatment category, by survival.

Treatment category	Child outcome frequency (%) n=113			Fisher exact test p-value
	Survived n=100	Died n=11	Not known n=2	<0.001
1st line treatment n=73	71 (97.5)	2 (2.5)	0 (0)	
1st & 2nd line treatment n=33	24 (72.5)	7 (21.5)	2 (2)	
1st, 2nd & 3rd line treatment n=7	5 (71.5)	2 (28.5)	0 (0)	

6. **The probability of the child's survival.**

b. Which clinical variables influenced the probability of the child's survival?

Interval data of weight and age and the categorical data of gender, treatment group, and length of stay (Table 4-19) were used to answer this question with binary logistical analysis applied (Table 4-51). . All children were cared for in a tertiary hospital, therefore this variable was removed from this analysis. There was no statistical significance in the probability of whether the child survived or not in relation to their gender (p=0.076), their age at chylothorax diagnosis (p=0.056) or their length of hospital stay if in categories 11-20 days or 51-365 days when compared to the reference group (p=0.168, p=0.424),(Table 4-51).

However, there were three clinical variables that were strongly associated with the child's survival or non-survival. There was a greater probability of children being in the survival group as their weight increased (p=0.038) although when compared to the reference group, those children receiving second and third line treatments had an increased probability of being in the non-survival group (p=0.025, p=0.015) (Table 4-51), and those children who stayed in hospital for 21-50 days had an increased probability of survival (p=0.47) when compared to the reference group.

Table 4-51 Children requiring cardiac surgery - Probability of child's survival compared to specific clinical variables.

Clinical Variable	Regression Parameter (B)	Standard Error (SE)	p-value
	(n=90)		
Age at chylothorax diagnosis (mths)	0.075	0.039	0.056
Weight (kgs)	-0.381	0.184	0.038
Gender (reference group -female)	-1.797	1.013	0.076
Length of stay -4-10 days (reference group)	-	-	0.120
Length of stay - 11-20 days	-2.321	1.682	0.168
Length of stay - 21-50 days	-3.723	1.875	0.047
Length of stay - 51-365 days	-1.489	1.863	0.424
Treatment category - 1st Line (reference group)	-	-	0.028
Treatment category - 2nd Line	3.091	1.379	0.025
Treatment category - 3rd Line	4.250	1.749	0.015

4.1.13 Summary of BPSU data

Chylothorax was most commonly reported in young children (2 months), with the majority (65.3%) developing the condition following cardiac surgery. Due to the substantial proportion of the total population that developed a chylothorax following cardiac surgery it was not unexpected that the cardiac sub-group analysis reflected that of the total population. Children were cared for in a variety of tertiary and district general hospitals in Strategic Health Authorities across the UK and clinicians most commonly confirm the development of a chylothorax by laboratory verification of the triglyceride content of the pleural fluid. Although a variety of treatment strategies are employed to manage the children, treatment with an intercostal pleural catheter and an MCT diet was most commonly reported. The majority of the children survived their hospital admission, although their stay tended to be lengthy.

4.2 Data Source 2 – Congenital Cardiac Audit Database (CCAD) Data

4.2.1 Case identification

CCAD provided data on children cared for in regional UK cardiac centres, who had developed a chylothorax within the study period. Data were provided in a Microsoft® Excel spread sheet categorising the chylothorax the child developed into one of six diagnostic levels or two procedural categories.

4.2.2 Demographic characteristics of the population

A total of nineteen children were reported as having developed a chylothorax. All were cared for in a tertiary cardiac centre, and the hospitals reporting the cases and their corresponding strategic health authority can be seen in Table 4-52).

Table 4-52 Chylothorax cases reported to the congenital cardiac audit database (CCAD)

Hospital	Strategic Health Authority and number of cases reported (n=19)
Tertiary Cardiac Hospital 3	SHA 10 (n=6)
Tertiary Cardiac Hospital 1	SHA 5 (n=4)
Tertiary Cardiac Hospital 4	SHA 12 (n=4)
Tertiary Cardiac Hospital 7	SHA 7 (n=2)
Tertiary Cardiac Hospital 10	SHA 9 (n=2)
Tertiary Cardiac Hospital 8	SHA 1 (n=1)

Eighteen of these nineteen children survived their hospital admission and their RACHS-1 Category can be seen in Table 4-53. There was no similarity in the type of surgery the children in Category 2 required, although as with the BPSU data, all three children in Category 6 required surgery for hypoplastic left heart syndrome, with the child that died being within this group.

Table 4-53 RACHS-1 Category of children who developed a chylothorax

Category	Number (%) (n=19)
Risk Category 1	1 (5.2)
Risk Category 2	10 (52.6)
Risk Category 3	5 (26.5)
Risk Category 4	2 (10.5)
Risk Category 5	0 (0)
Risk Category 6	0 (0)
Surgical procedure not recorded	1 (5.2)

4.2.3 Summary of CCAD data

There was poor submission of data to CCAD regarding those children who developed a chylothorax following cardiac surgery. When comparing the number of reported cases in the cardiac sub analysis from the BPSU data (Section 4.1.12), to the number of cases CCAD were informed of, only 16.8% had been reported.

All children had been cared for in a tertiary cardiac hospital and the RACHS-1 Category of the CCAD children who developed a chylothorax generally reflected those of the larger cardiac surgical procedural group in the BPSU data, where children had required cardiac procedures in Categories 2 and 3.

4.3 Data Source 3 – Hospital Episode Statistics (HES) Data

4.3.1 Case identification

HES identified 504 children in England within the study period that had an ICD-10 code categorised as J94.0, J94.8, J94.9, I89.8 or I89.9 (Section 3.5.8.3). This dataset included prevalent cases of any child with a diagnosis of chylothorax recorded as either a primary or secondary condition or co-morbidity. Multiple treatment episodes for a child during the same admission were removed resulting in 276 cases, a considerably higher number than those reported from England via the BPSU (n=150).

4.3.2 Demographic characteristics of the HES children

The following section describes the demographic and clinical data of the HES children with Table 4-54 and Table 4-55 providing more detail on the information available. The median age of the population was 19 months with 167 (60.5%) being male. The majority of the children were from a white ethnic background, n=184 (66.5%), with multiple ethnicities being represented.

Table 4-54 Demographic characteristics of children reported to HES as having developed a chylothorax

Demographic characteristic		Number (%) (n=276)
Gender:	Male	167 (60.5)
Ethnicity:	White	184 (66.5)
	Asian or Asian British	29 (10.5)
	Not Known	27 (10)
	Other	12 (4.5)
	Black or Black British	11 (4)
	Mixed	10 (3.5)
	Chinese	3 (1)

Table 4-55 Clinical characteristics, median, mean and confidence interval, of the children reported to HES

Clinical feature	Median (range) [IQR] n=276	Mean [95% CI for mean]
Age in months at time HES data generated (30th June 2011)	19 (1 – 212) [66]	53.95 [46.38-61.53]

4.3.3 Diagnostic groups of those children who developed a chylothorax

Chylothorax was most commonly recorded in conjunction with cardiac surgery n=113 (41%), with non-cardiac medical conditions n=72 (26%) being the second most common co-morbidity (Table 4-56).

Table 4-56 Diagnostic groups of those children reported to HES, who developed a chylothorax

Primary diagnosis	Number (%) (n=276)
Cardiac Surgical	113 (41)
Medical (non-cardiac)	72 (26)
Neonatal Congenital	36 (13)
Neonatal Other	19 (7)
Surgery (non-cardiac)	13 (4.5)
Cardiac Medical	12 (4.5)
Oncology / Haematology	7 (2.5)
Trauma	4 (1.5)

Of those 113 children who had a primary diagnostic category of cardiac surgery, the surgical repairs most commonly required were for Tetralogy of Fallot n=18 (16%), Hypoplastic Left Heart Syndrome n=17 (15%), Atrio-ventricular Septal Defect n=12 (11%) and Coarctation of the Aorta n=9 (8%). These comprised 50% of this total category.

Of the Medical (non-cardiac) category the majority of the children had a primary diagnosis categorised as 'other specific non-infective disorder of the lymphatic vessels and lymph node' (I89.8) n= 20 (28%) and 'chylous effusion' (J94.0) n= 7 (10%).

4.3.4 Hospitals providing care for children who developed a chylothorax

Seventy-one hospitals from across England reported caring for children who developed a chylothorax. Table 4-57 identifies the top eleven reporting hospitals which account for n=190 (69%) of the reported cases.

Table 4-57 Hospitals and the corresponding number of children reported to HES as having developed a chylothorax

Top 11 Hospitals reporting most chylothorax case in England		Number (%) (n=276)
Tertiary Cardiac Hospital 9	(SHA 7)	46 (16.5)
Tertiary Cardiac Hospital 6	(SHA 2)	22 (8)
Tertiary Cardiac Hospital 1	(SHA 5)	21 (7.5)
Tertiary Cardiac Hospital 10	(SHA 9)	20 (7.5)
Tertiary Cardiac Hospital 2	(SHA 3)	16 (6)
Tertiary Cardiac Hospital 3	(SHA 10)	16 (6)
Tertiary Cardiac Hospital x	(SHA 4)	14 (5)
Tertiary Cardiac Hospital 5	(SHA 7)	11 (4)
Tertiary Combined Hospital x	(SHA 7)	10 (3.5)
Tertiary Cardiac Hospital 8	(SHA 1)	7 (2.5)
Tertiary Cardiac Hospital x	(SHA 4)	7 (2.5)
Other (Total of 60 hospitals)		86 (31)
Total		**276 (100)**

When mapping the hospitals to their corresponding Strategic Health Authority (SHA), children were cared for in all SHA across England, with the majority in London n=92 (33.5%), (Table 4-58).

Table 4-58 Primary diagnoses of the children reported to HES and the SHA providing their care

(Comparison with the number of cases reported by SHA to BPSU).

Strategic Health Authority	Primary Diagnostic Category Number (%) (n=276)									BPSU Cases in England by SHA
	Neonatal Congenital	Neonatal Other	Cardiac Medical	Cardiac Surgical	Medical (non-cardiac)	Haematology / Oncology	Surgical (non-cardiac)	Trauma	Total	
SHA 1	4 (1.4)	1 (0.4)	2 (0.7)	3 (1.5)	0 (0)	0 (0)	1 (0.4)	2 (0.7)	**13 (4.5)**	**10 (5.8)**
SHA 2	4 (1.4)	2 (0.7)	1 (0.4)	15 (5.4)	10 (3.6)	0 (0)	1 (0.4)	1 (0.4)	**34 (12)**	**14 (8.1)**
SHA 3	1 (0.4)	3(1.1)	1 (0.4)	11 (4.)	6 (2.2)	0 (0)	0 (0)	0 (0)	**22 (8)**	**30 (17.3)**
SHA 4	2 (0.7)	0 (0)	1 (0.4)	11 (4.)	10 (3.6)	0 (0)	2 (0.7)	0 (0)	**26 (9.5)**	**10 (5.8)**
SHA 5	3 (1.1)	2 (0.7)	3 (1.1)	12 (4)	6 (2.2)	1 (0.4)	2 (0.7)	0 (0)	**29 (10.5)**	**24 (13.8)**
SHA 6	2 (0.7)	2 (0.7)	0 (0)	2 (0.7)	5 (1.8)	0 (0)	0(0)	0 (0)	**11 (4)**	**11 (6.4)**
SHA 7	18 (6.5)	3 (1.1)	5 (1.8)	28 (10.1)	24 (8.7)	5 (1.8)	9 (3.3)	0 (0)	**92 (33.5)**	**17 (19.8)**
SHA 8	2 (0.7)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	**3 (1)**	**13 (7.5)**
SHA 9	1 (0.4)	0 (0)	0 (0)	17 (6.2)	5 (1.8)	0 (0)	0 (0)	0 (0)	**23 (8.5)**	**2 (1.2)**
SHA 10	3 (1.1)	1 (0.4)	2(0.7)	11 (4)	5 (1.8)	0 (0)	1 (0.4)	0 (0)	**23 (8.5)**	**19 (11)**
Total	**40 (14.5)**	**14 (5)**	**15 (5.5)**	**111 (40)**	**71 (26)**	**6 (2)**	**16 (6)**	**3 (1)**	**276 (100)**	**150 (87%)**

4.3.5 Child's discharge destination or outcome

Although some of the children remained in hospital, with treatment continuing when the data were provided, n=189 (68.5%) had been discharged, however n=17 (6%) had not survived (Table 4-59).

Table 4-59 Children's discharge destination or outcome

Child's discharge destination or outcome	Number (%) (n=276)
Survived and discharged	189 (68.5)
Treatment continuing	66 (24)
Died	17 (6)
Not known	4 (1.5)

4.3.6 Sub-analysis of children reported to both HES and BPSU (England only data)

4.3.6.1 Case identification

As identified in the study methodology, both HES and the BPSU provided identifiable data for those children reported to have a chylothorax within the study period. Those children reported to the BPSU from England were extracted from the entire BPSU data and matched to those reported by HES. HES reported n=276 children and of the BPSU population, n=150 were from England. When these cases were compared, n=63 children could be mapped identically. These children corresponded to 23% of all the HES reported cases and 42% of the children reported to the BPSU from England. Therefore, 58% of children who developed a chylothorax in England were not reported to HES. An analysis of the 63 children who were identified in both datasets is presented in the following section, together with the findings from the capture-recapture review.

4.3.6.2 Capture-recapture

The two source capture:recapture technique was undertaken between the HES data and those children reported via the BPSU to have developed a chylothorax in England (Section 3.5.8.3). Hook & Regal's (1995) statistical formula (Appendix 5) was applied to estimate the number of additional chylothorax cases that could have been missed by the data collection and hence identify the 'true' population of children with chylothorax in England during the study period. This resulting total population far exceeded the number of children reported by either the HES or BPSU data sources and this was likely to relate to three key breaches in the analysis assumptions. Firstly the HES data included codes that might not have been specific to chylothorax (Table 3-6) and could not be separately identified. Secondly, the HES data included both incident and prevalent cases and lastly the HES data included both primary and secondary diagnoses. It was therefore highly likely that these two populations were substantially different and therefore this planned analysis was not considered suitable for presentation.

4.3.6.3 Demographic characteristics of the 'matched' children

Within this sub-group of children, more boys than girls were diagnosed with a chylothorax and the majority were from a white ethnic background (Table 4-60).

Table 4-60 Demographic characteristics of the HES and BPSU matched children

Demographic characteristic		Number (%) (n=63)
Gender:	Male	37 (58.7)
Ethnicity:	White	53 (84.1)
	Asian or Asian British	8 (12.7)
	Black or Black British	2 (3.2)

The median age, range and interquartile range of the children at the end of the study (Table 4-61) duplicated that of the entire population in the BPSU data

(Table 4-2), but the children were notably older in the HES data (Table 4-55), where the median was 19 months, range 1-212 and interquartile range 66.

Table 4-61 Clinical feature, age at diagnosis (months) median, mean and confidence interval of the HES and BPSU matched children

Clinical feature	Median (range) [IQR}	Mean [95% CI for mean]
Age at diagnosis (months)	2 (1-174) (14) (n=63)	15.44 [7.99-22.90]

4.3.6.4 Diagnostic groups of those children who developed a chylothorax

As with analysis undertaken in previous sections, development of a chylothorax was most commonly linked with cardiac surgery n=44 (69.8%), neonatal congenital and surgical (non-cardiac) n=6 (9.5%) cases (Table 4-62). No child was reported with a classification of trauma or oncology / haematology within this sub-group.

Table 4-62 Diagnostic groups of those matched children who developed a chylothorax

Primary diagnosis	Number (%) (n=63)
Cardiac Surgical	44 (69.8)
Surgery (non-cardiac)	6 (9.5)
Neonatal Congenital	6 (9.5)
Neonatal Other	3 (4.8)
Cardiac Medical	2 (3.2)
Medical (non-cardiac)	1 (1.6)
Not Known	1 (1.6)

4.3.6.5 Hospitals reporting chylothorax cases to both HES and BPSU

Twenty-three hospitals from across England reported children who developed a chylothorax to both HES and BPSU. Table 4-63 identifies the primary hospitals that reported caring for 75% (n=47) of the 63 matched cases. Assuming the number of children reported via the BPSU as having developed a chylothorax is correct, the data in Table 4-63 suggests that approximately one-third are coded correctly and reported accurately to HES.

All Strategic Health Authorities across England reported children who developed chylothorax to both HES and BPSU, with SHA 3 and SHA 10 providing most of the 'matched' data (Table 4-64). However the number of 'matched' cases corresponded poorly to the number of children reported via the BPSU.

Table 4-63 Hospitals reporting the matched HES and BPSU chylothorax cases

(Comparisons provided with total HES, BPSU and CCAD reported cases)

Hospitals reporting matched cases to HES & BPSU	Matched HES & BPSU reported cases	HES reported cases	BPSU reported cases (Top 10 hospitals)	CCAD reported cases
Tertiary Cardiac Hospital 1	13	21	31	4
Tertiary Cardiac Hospital 2	8	16	22	0
Tertiary Cardiac Hospital 3	8	16	15	6
Tertiary Cardiac Hospital 4	n/a	n/a	14	4
Tertiary Cardiac Hospital 5	5	11	10	0
Tertiary Cardiac Hospital 6	8	22	10	0
Tertiary Cardiac Hospital 7	1	0	8	2
Tertiary Cardiac Hospital 8	2	7	8	1
Tertiary Cardiac Hospital 9	0	46	5	0
Tertiary Cardiac Hospital 10	2	20	4	2
Tertiary Cardiac Hospital	0	14	-	0
Tertiary Cardiac Hospital	0	7	-	0
Tertiary Combined Hospital	0	10	-	n/a
Other (15 Hospitals) Other (39 Hospitals) Other (60 Hospitals)	16 - -	- - 86	- 46 -	n/a n/a- n/a
Total	**63**	**276**	**173**	**19**

Table 4-64 Primary diagnosis of the matched HES and BPSU children and the SHA providing their care

(Comparison provided with all HES cases and BPSU cases reported from England)

Strategic Health Authority	Primary diagnostic category Number (%) of 'matched' cases							All HES cases by SHA Number (%)	BPSU Cases in England by SHA Number (%)
	Neonatal Congenital	Neonatal Other	Cardiac Medical	Cardiac Surgical	Medical (non-cardiac)	Surgical (non-cardiac)	Total		
SHA 1	2 (3.2)	0 (0)	0 (0)	3 (4.8)	0 (0)	0 (0)	**5 (7.9)**	**13 (4.5)**	**10 (5.8)**
SHA 2	1 (1.6)	0 (0)	0 (0)	6 (9.5)	0 (0)	0 (0)	**7 (11.1)**	**34 (12)**	**14 (8.1)**
SHA 3	1 (1.6)	0 (0)	0 (0)	12 (19)	0 (0)	1 (1.6)	**14 (22.2)**	**22 (8)**	**30 (17.3)**
SHA 4	0 (0)	0(0)	1 (1.6)	2 (3.2)	0 (0)	0 (0)	**3 (4.8)**	**26 (9.5)**	**10 (5.8)**
SHA 5	0 (0)	0 (0)	1 (1.6)	6 (9.5)	0 (0)	0 (0)	**7 (11.1)**	**29 (10.5)**	**24 (13.8)**
SHA 6	0 (0)	0 (0)	0 (0)	3 (4.8)	1 (1.6)	0 (0)	**4 (6.3)**	**11 (4)**	**11 (6.4)**
SHA 7	0 (0)	3 (4.8)	0 (0)	0 (0)	0 (0)	2 (3.2)	**5 (7.9)**	**92 (33.5)**	**17 (19.8)**
SHA 8	1 (1.6)	0 (0)	0 (0)	3 (4.8)	0 (0)	2 (3.2)	**6 (9.5)**	**3 (1)**	**13 (7.5)**
SHA 9	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	0 (0)	**1 (1.6)**	**23 (8.5)**	**2 (1.2)**
SHA 10	2 (3.2)	0 (0)	0 (0)	8 (12.7)	0 (0)	1 (1.6)	**11 (17.5)**	**23 (8.5)**	**19 (11)**
Total	**7 (11.1)**	**3 (4.8)**	**2 (3.2)**	**44 (69.8)**	**1 (1.6)**	**6 (9.5)**	**63 (100)**	**276 (100)**	**150 (87)**

4.3.6.6 The child's discharge destination or outcome for the 'matched' children who developed a chylothorax.

Similar to data provided in other sections (Sections 4.1.9; 4.1.12.7) some of the children remained in hospital with treatment continuing when the data were provided. However, n=48 (76.2%) had been discharged, but n=6 (9.5%) had not survived (Table 4-65).

Table 4-65 Child's discharge destination or outcome for the matched children vs. cardiac surgical and BPSU children

Child's discharge destination or outcome	Matched children Number (%) (n=63)	BPSU cardiac surgical children Number (%) (n=113)	All BPSU children Number (%) (n=173)
Survived & discharged	48 (76.2)	82 (72.5)	117 (67.5)
Treatment continuing	7 (11.1)	18 (16)	29 (17)
Died	6 (9.5)	11 (9.5)	22 (12.5)
Not known	2 (3.2)	2 (2)	5 (3)

4.3.7 Summary of HES data

In comparison to the three other data sources, significantly more children, from a greater number of hospitals were reported to HES as having developed a chylothorax.

The most commonly linked primary diagnosis for the children reported to HES was cardiac surgical, and this reflected the BPSU cases. Despite only 63 chylothorax cases matching identically between the HES data (n=276) and the BPSU data (England cases) (n=150), both datasets reported 113 children as developing a chylothorax following cardiac surgery. Data analysis of this sub-group largely reflected those found in the BPSU data, although the second most common diagnostic group was jointly a neonatal congenital and surgical (non-cardiac) link (Table 4-62), neither which were reflected by the BPSU data.

The number of children reported who did not survive was lower within the HES data (n=17, 6%), (Table 4-59) in comparison to the BPSU data (n=22, 12.5%), (Table 4-18).

4.4 Data Source 4 – Paediatric Intensive Care Audit Network (PICANet) Data

4.4.1 Case identification

PICANet provided data on children with a primary diagnosis or co-morbidity of chylothorax, with cases being identified via their national paediatric intensive care audit collection tool. Hospitals contributing to this UK data collection included all UK Tertiary Cardiac and Tertiary Combined Hospitals (Section 4.1.6).

4.4.2 Demographic characteristics of the children

Forty-two children who developed a chylothorax during the study period were reported to PICANet, with all but one, being cared for in a tertiary cardiac centre in England or Scotland (Table 4-66). This reflects the organisations submitting data to PICANet, however the number of children reported to them was <40% of those reported via the BPSU to have required cardiac surgery, all of whom would have been cared for in intensive care. The median age of the children was ten months with a range of ≤1 month to 180 month (Table 4-67).

Table 4-66 Children reported to PICANet as having developed a chylothorax

Hospital category	SHA and number of children	
Tertiary Cardiac Hospital 1	SHA 5	n=10
Tertiary Cardiac Hospital 2	SHA 3	n=9
Tertiary Cardiac Hospital 10	SHA 9	n=9
Tertiary Cardiac Hospital 9	SHA 7	n=5
Tertiary Cardiac Hospital 6	SHA 2	n=3
Tertiary Cardiac Hospital 5	SHA 7	n=2
Tertiary Cardiac Hospital 7	SHA 7	n=2
Tertiary Cardiac Hospital 3	SHA 10	n=1
Tertiary Combined Hospital	SHA 2	n=1
Total		**n=42**

Table 4-67 Clinical feature, median, mean and confidence interval of children reported to PICANet as having developed a chylothorax

Clinical feature	Median (range) [IQR}	Mean [95% CI for mean]
Age in months at time PICANet data generated (30th June 2011)	10 (0 - 180) [10] (n=42)	18.14 [9.15-27.13]

4.4.3 Summary of PICANet data

When reviewing the number of chylothorax cases individual hospitals submitted to PICANet (Table 4-66) in comparison to those they reported to the BPSU (Table 4-12), there was a significant difference, with only 40% of the children having been reported to PICANet. With the majority of these hospitals being tertiary cardiac centres, children would most likely have been cared for in the intensive care unit and as such reporting of these cases should have been to both data sources.

The median age of the children reported to PICANet was higher (10 months) than both the entire population (2 months), (Table 4-2, Section 4.1.2) and the cardiac surgical sub group (6 months), (Table 4-33) but lower than the HES cases (19 months), (Table 4-55).

4.5 Chapter summary

The above section provides a detailed analysis of the data provided from each of the four data sources, together with the calculated incidence for chylothorax development in the UK and England. Table 4-68 provides an overview of the number of cases reported by each data source (BPSU, CCAD, HES and PICANet) and the hospital that reported the cases. The number of children reported by each data source differs and this could be associated with a variety of factors including the differing population each data source targeted (Table 3-1, Section 3.3.4), poor accuracy in documenting co-morbidities, poor reporting of secondary codes or other.

In the following chapter both the methodology and results will be discussed and where possible, the findings will be placed in context of similar populations reported in the literature.

Table 4-68 Hospitals reporting children who developed a chylothorax, and the number of cases reported to each data source.

Hospital	Data source with reported case numbers and % comparison to BPSU data numbers			
	Data Source 1 BPSU	Data Source 2 CCAD	Data Source 3 HES	Data Source 4 PICANet
Tertiary Cardiac Hospital 1	31	4	21	10
Tertiary Cardiac Hospital 2	22	0	16	9
Tertiary Cardiac Hospital 3	15	6	16	1
Tertiary Cardiac Hospital 4	14	4	n/a	0
Tertiary Cardiac Hospital 5	10	0	11	2
Tertiary Cardiac Hospital 6	10	0	22	3
Tertiary Cardiac Hospital 7	8	2	0	2
Tertiary Cardiac Hospital 8	8	1	7	0
Tertiary Cardiac Hospital 9	5	0	46	5
Tertiary Cardiac Hospital 10	4	2	20	9
Tertiary Cardiac Hospital	0	0	14	0
Tertiary Cardiac Hospital	0	0	7	0
Tertiary Combined Hospital	0	0	10	0
Tertiary Combined Hospital	0	0		1
Other	46 (49 hospitals)	0	86 (60 hospitals)	0
Total	**173**	**19**	**276**	**42**

5. Discussion

5.1 Summary of the findings

This study was developed following observation from health professionals that the frequency of chylothorax development in children in the UK was unknown and that management strategies prescribed and administered to treat these children were varied and based on limited evidence. Additionally, both the duration of hospital stay and the outcome and hospital discharge destination of these children were unclear. This information led to speculation that treatment strategies and care for these individuals may have been suboptimal.

A review of the literature highlighted a paucity of international research specifically focusing on this patient group and the evidence that was available was reported primarily in a number of small scale retrospective cohort studies (Beghetti *et al.* 2000;Bond *et al.* 1993;Cannizzaro *et al.* 2006;Katanyuwong *et al.* 2009;Milonakis *et al.* 2009;Nguyen *et al.* 1995) and case-series reports (Biewer *et al.* 2010;Doerr *et al.* 2005;Sersar 2011). Existing evidence suggested that chylothorax development in children occurs largely in the neonatal period and following cardiac surgery, although the poor quality of evidence resulted in conclusions being unclear. Hence, detailed data were required to establish the incidence of chylothorax, related conditions and to obtain definitive information on the current treatment strategies these children received, duration of hospital stay and their discharge destination or outcome. These detailed data were collected via this observational, descriptive surveillance study of children who developed a chylothorax in the UK. This is the largest reported children's chylothorax study and the first country-wide dataset reported internationally being considerably larger than any other previously reported study in the UK.

The study primarily focused on a prospective national surveillance design, with additional data triangulation achieved by utilising retrospective data from three additional sources, CCAD, HES and PICANet to verify the primary data

collection. Prior to the study commencing, both REC and NIGB approval were obtained (Section 1.3).

From the prospective data collected via the BPSU, information was received on 173 children cared for in forty-nine hospitals across the UK. The data identified development of chylothorax in children in the UK is not common, with a national incidence of 1.4 in 100,000 (0.0014%), slightly increased to 1.6 in 100,000 (0.016%) in infants ≤12 months. The majority of children develop a chylothorax following cardiac surgery, with a reported UK incidence of 3,100 in 100,000 (3.1%).

Descriptive analysis of the data revealed the same conditions to be linked to chylothorax development in this national population study as were reported in the published cohort studies and case-series papers, i.e. cardiac surgery and neonatal abnormalities. A substantial proportion of surgery for congenital cardiac abnormalities in children is undertaken within the first year of life (Knowles *et al.* 2012) and this combined with the neonatal group, is reflected in the median age of presentation of two months.

The variation in diagnostic investigations used to confirm the chylothorax was unexpected. Although the majority gained laboratory confirmation, some used more subjective diagnostic criteria including the speed of accumulation of the effusion and clinical suspicion. Although evidence was not extensive, there was consistency within the literature that biochemical analysis of the pleural fluid was advised (Buttiker *et al.* 1999;Helin *et al.* 2006), however this was not unanimously undertaken within this study population. Conservative management strategies of an intercostal pleural catheter and an MCT diet were the favoured administered treatments, although variation existed in the duration of time these continued for.

The length of stay for these individuals is prolonged and therefore the impact on the child, their family and hospital resources are likely to be significant.

The reported mortality of 12.5% was high. These data confirm the potential importance of chylothorax, despite its relative rarity, particularly in those patient groups most at risk.

5.2 Incidence

This is the first study to provide national incidence data for chylothorax development in children hence no other comparative data exists. The true incidence of chylothorax development in children prior to this study was unknown, with reported incidence being reliant on poor quality evidence due to small sample numbers, study design and retrospective data. The incidence of chylothorax development in the UK paediatric population was 1.4 in 100,000 (0.0014%) and in infants ≤12 months 1.6 in 100,000 (0.016%). The increased incidence in younger children corresponds to the observed association between chylothorax development, neonatal conditions and cardiac surgery, and is consistent with the rate reported in Rocha *et al's* (2006) multi-centre study of neonates in Portugal.

Chylothorax incidence in children following cardiac surgery was previously reported as ranging from 0.5% - 9.2% based on single centre or a small number of combined centres' data, with an average incidence of 3.2%, and a median of 2.2% (Table 2-1, Table 2-2 and Table 2-3). This study reports a national incidence of chylothorax within this group of children as being consistent with the average at 3.1%, with England having a slightly higher rate at 3.3%. This slightly higher incidence in England probably reflects the movement of children from Wales to England if cardiac surgery is required. Again, the incidence in this study is consistent with previous literature, despite the poor quality of previous studies. Calculation of individual hospital incidence was not possible with the data collected. PICANet did provide the total number of cardiac surgical procedures undertaken in individual hospitals across the UK (Table 4-6) and collated the number of children who developed a chylothorax cared for in a tertiary cardiac hospital, (Table 4-12). However, to make an assumption that these children all developed the condition following cardiac surgery would be inaccurate.

Whilst the increase in the complexity of cardiac surgical operations reported in the UK (NICOR 2013) could have reflected an increased chylothorax incidence, the improvement and developments in clinical expertise and health technology over the last decade, together with the centralisation of paediatric cardiac services where clinical expertise is concentrated to a limited number of hospitals, may offer a potential explanation for the incidence remaining low.

Individual SHA incidence for chylothorax development following cardiac surgery ranged from 0.6%–8.2%. Although this is a wide variation, these results are consistent with all previously reported incidence rates and probably reflects the complexity of cardiac surgery offered in some centres, an aspect identified by others as a risk factor for chylothorax development (Chan *et al.* 2005;Mery *et al.* 2013). This variation in incidence requires further investigation and future monitoring and assessment of chylothorax morbidity across all centres, with the establishment of national guidance for acceptable limits of variation, data which is already provided by NICOR for primary cardiac surgical procedure mortality within the UK (NICOR 2013).

Due to a lack of comparable data, it is not possible to accurately compare the low chylothorax incidence in the UK neonatal population (0.004%, 4 in 100,000) with other studies. Although Caserio *et al* (2010) and Rocha *et al* (2006) do report on congenital chylothorax development in neonates, neither study includes neonates with an acquired chylothorax. Despite this discrepancy, the neonatal incidence reported in this study was considerably lower than that reported in either of the above two studies.

The marked variation in incidence rates between children who developed a chylothorax in the UK following cardiac surgery (3,100 in 100,000) (Section 4.1.3.2) and those with a medical neonatal association (4 in 100,000) (Section 4.1.3.3) is considerable. Further investigation and data analysis on the relevance cardiothoracic surgery, surgical procedures, techniques and or expertise have on chylothorax development in children are required.

Overall the data show a low incidence of chylothorax occurring in all children which would be consistent with it being a rare condition. Whilst the incidence following cardiac surgery reflects previous data, it is perhaps higher than expected given there is still a relatively low rate in the congenital neonatal group. This information has service planning and resource management implications for designated children's cardiac surgical centres, adding to the financial burden placed on these services.

5.2.1 Data completeness

Through the national prospective BPSU surveillance scheme, the intention was to gather data on all children who developed a chylothorax in the UK. The BPSU study methodology is a well-established active surveillance scheme that reports an overall orange card compliance rate for 2011 (Section 3.3.2), calculated as a proportion of orange cards returned, as 91.4% (BPSU. 2012). Following the reporting of a child whose condition is under investigation, the process is then dependent on clinicians completing a questionnaire. In this study which required engagement from multiple clinical specialities in a large number of hospitals across the UK, the questionnaire completion rate following the reporting of a child with a chylothorax via the orange card system was 86.5% (n=219) (Figure 4-1), demonstrating a high completion rate. There were however a proportion of identified children 'unable to be followed-up' (n=34), although half of these were from one hospital, where there appeared to be some miscommunication regarding which clinicians were reporting the cases, leading to a potential risk that these were duplicate rather than lost cases. If they were true cases and these children died, there would be the potential for considerable bias within the final data set.

This study demonstrated a high response rate that provided data on a greater number of children than either the CCAD or PICANet data sources, although the overall response rate was 5% lower than the BPSU national average expected from the distribution of the orange cards. Additionally, the study investigator was aware that there was a small number of missing cases due to

either the absence of or a poor response from centres with known cases yet minimal or no reporting. However, although this study's reported population numbers and the incidence is most likely to be a slight under estimation of the true number, the data does provide a robust indicator of incident cases within the BPSU target population.

The choice of research methodology meant it was not possible for the study investigator to access any child's notes, or to have direct patient or carer contact, restricting their ability to clarify individual information and relying on notifying clinicians to provide the requested data. Whilst most clinicians fully completed the questionnaire, for those who did not, there was a poor response to any request for missing data, possibly reflecting the time pressures on clinical staff and the challenges in obtaining information once the child had been transferred home or to an alternative hospital. There were no specific patterns to data that were missing, although the start and completion dates for treatment options or management strategies were the most commonly omitted. This information should have been recorded in the child's health records, on their drug prescription chart or fluid chart, and should have been easily accessible.

Data triangulation was used to assess the quality and completeness between the data sources and identify any dissonance between them. When comparing the number of cases reported via the BPSU (n=173), to those reported by CCAD (n=19) and PICANet (n=42), irrespective of the differences in data collection sources, case numbers reported by the latter two were substantially lower than would have been expected. Data provided by CCAD to the investigator presented the child's primary diagnosis together with up to five additional co-morbidities and as a result the chylothorax diagnosis was visibly identifiable within each child's submitted dataset. Nonetheless, the fact so few children with chylothorax were reported by CCAD questions the accuracy of the data submitted by hospitals and requires further investigation, as well as a review of the implications it has for practice and service planning. This is not an area highlighted as a concern within the literature, indeed between 1st April 2000 and 31st March 2002, Westaby *et al.* (2007) identified an overall data provision

for CCAD datasets matched against benchmarked procedures as being 96.8%, with data completeness for individual fields ranging from 75%-100%. However, apart from mortality numbers and operations undertaken, they do not specify what additional procedures were matched. These results strongly contrast with the experience of the CCAD data provision in this study, suggesting a high level of data completeness and providing a positive picture of accuracy and totality for the data, not experienced here.

The robustness of the CCAD data suggested by Westaby *et al.* (2007) was not demonstrated by any site within this study, but could possibly be explained by a number of differing factors. CCAD only commenced data collection from centres in 2000, and therefore Westaby's results are based on initial CCAD data collection variables which may have only included primary diagnosis or procedure and mortality data, rather than secondary diagnoses or co-morbidity data such as the development of a chylothorax. Similarly, this co-morbidity data may have been poorly reported with a lack of awareness by personnel within hospitals of the need, or value in reporting. Indeed this inaccuracy in documenting ICD-10 co-morbidity data is highlighted by Levy *et al* (1999) and was discussed in Section 3.5.8.1. Furthermore, a lack of understanding of how to effectively use the CCAD database, a lack of personnel or senior support to aid completion of the database in a timely fashion, and a concern that chylothorax as a co-morbidity may be seen as an adverse event which may lead to a reluctance to report, could all be reasons why there was dissonance between this and the BPSU datasets. Furthermore, despite the high completion rates identified by Westaby *et al.* (1997), many units across the country were found to be poorly funded to collect or validate CCAD data effectively (Westaby *et al.* 2007). Therefore questions remain on how these high completion rates were achieved, who collected and submitted the data, and which factors were in place at the time to encourage completion.

The small number of case reported by PICANet in part reflects data solely being collected from paediatric intensive care units within the UK (Table 3-7). However data numbers should largely be comparable with the BPSU cardiac sub-group (n=113), as the majority of these children will have been cared for

in an intensive care environment, with the odd exception of a child who may have developed a chylothorax following discharge to the ward. However, PICANet was only able to provide data on 42 children who had developed a chylothorax whilst in intensive care, which equates to 37% of the BPSU cardiac surgical children. As stated above, this is probably reflective of chylothorax being a co-morbidity rather than a primary diagnosis and is likely to demonstrate the poor completion by clinical staff of this secondary diagnostic information.

The comparative analysis of the HES data with the BPSU (England) data suggests an incomplete HES dataset for this co-morbidity, with 58% of children not having been reported to HES, therefore demonstrating a substantial under-estimate of the incident cases. With data submission to HES being reliant on clinical coders within hospitals interpreting and submitting information obtained from the child's discharge summary, considerable bias and variation in practice and quality is possible, an issue discussed and debated in Section 3.5.8.1. The inconsistency in reporting co-morbidities to HES is a well reported (Campbell *et al.* 2001;Levy *et al.* 1999) however this considerable lack of overlap between two major datasets poses questions around their accuracy and reliability and has considerable implications when these dataset are used to inform health service developments and government health funding. Further investigation into these discrepancies is therefore needed as there are significant social, political and clinical implications of relying on the accuracy of faulty data sets such as these (Independent Reconfiguration Panel 2013).

It is anticipated that the greater number of children reported via HES in comparison to the BPSU primarily relates to the combination of both prevalence and incidence cases present within the former data. Although it was not possible to differentiate between HES incident and prevalence cases, based on the child's method of discharge it was possible to remove duplicate datasets that related to the same patient episode, and therefore many of the prevalence cases. However some children reported by HES will have been diagnosed with a chylothorax prior to the study commencing and identifying these children within the data is not possible. Additionally, the number of differing HES

chapter codes requested increased the inaccuracy of these data. To address this, a more precise coding application to HES is required, where data are requested solely on code(s) that specifically identify chylothorax. Once this has been achieved and more precise data obtained a future analysis of the resulting data will be possible and the capture:recapture incidence calculated.

The 'true' population of children with chylothorax in England identified following the capture-recapture analysis, is therefore likely to differ to that identified in either the HES or BPSU data sources (Section 4.3.6.2). The fact that HES data will include both prevalent and incidence cases is discussed above and will contribute to the higher figure. However, to gain a more accurate 'true' population further consideration needs to be given to the HES data to ensure there is sole identification of incidence rather than prevalence cases and any time interval that occurs between a hospital coding a child's admission and discharge and HES receiving this data is accounted for. Furthermore, as discussed above, additional refining of the chapter codes is needed to more specifically identify chylothorax. However, even allowing for data completeness issues, the number of children reported by HES suggests there are continuing resources and morbidity issues for these children, which may not be reflected in the incidence data. These aspects are of considerable importance to the child, family and service providers and require further investigation.

Despite the differing numbers of children reported to HES and the BPSU as having developed a chylothorax, both datasets reported the same number of children having a primary diagnostic category related to cardiac surgery (n=113). However, although limited identifiable data were available for both data sets only 63 children could be identically matched. This discrepancy may be associated with the number of children who were known to develop a chylothorax but were not reported to the BPSU, although the difference of fifty cases is high. The fact that some children reported by HES as having developed a chylothorax following cardiac surgery are likely to be prevalence cases diagnosed outside the study period and/or may have had alternative

diagnoses but were reported as cases due to the request for multiple ICD-10 chapter codes, could also contribute to this discrepancy.

Although this study aimed to collect data on an entire population of children who developed a chylothorax in the UK, the resulting data identifies the study has captured a sample of this population. This sample is heterogeneous with children varying in age and ethnicity, they have varying primary diagnoses and were cared for in multiple centres across the UK. The sample size far exceeds that of previous studies and whilst the total population reported in this study may be a slight under-estimation due to missing cases, the research questions regarding the demographic and clinical features of the children, the management strategies prescribed and administered to treat them, their length of hospital stay and discharge destination or outcome, can be answered with the data generated from this study. This study has therefore undoubtedly provided the best estimate thus far of incidence in this country and in addition has the capability to provide an estimate of the likely degree of error in this dataset due to the use of multiple data sources. Whilst questions can be raised regarding the true completeness of the population planned for investigation, unless centres with suspiciously small numbers of cases are caring for these children in a fundamentally different way to those reporting more complete data, this data will be highly representative of the total.

5.3 Population characteristics

The diagnostic categories of children who developed a chylothorax within this study had all been previously identified within the literature, however the most common category was cardiac surgery (65.3%). This group had been the primary focus of the majority of previously published cohort studies and case-series papers, hence the results from this study support existing literature. The remaining 34.7% of children have previously being poorly studied and therefore this study provides primary new data for this patient sub-group.

Slightly more boys than girls developed a chylothorax and this reflects previous studies where authors have reported on the gender of their sample (Biewer *et al.* 2010;Chan *et al.* 2005;Chan *et al.* 2006;Doerr *et al.* 2005). The ethnicity of the entire BPSU population reflects that of the England and Wales 2011 census (Office for National Statistics 2012) with the majority of the children being white followed by Asian or Asian British (Table 4-1). The median age of the entire BPSU population was several months younger than the cardiac surgical sub-group (two months vs. six months), however this increased to nineteen months in the HES data. The variations and possible under-reporting within these two data sets has been discussed above. With neonatal congenital chylothorax being the second most common diagnostic category (12.5%), the younger presenting age of these children was not unexpected. Furthermore, these data provides the first evidence of the percentage of children who had a congenital diagnostic category linked to their chylothorax (Section 2.6.2). The slightly older age of the children in the cardiac surgical sub-group again was not unexpected as this reflects the variable time frame, usually within the first year of life, when those born with congenital heart disease undergo surgical intervention (Knowles *et al.* 2012).

Of note was the considerable difference in the median age of the children with cardiac conditions who developed a chylothorax, with those with medical diagnoses having a substantially higher median age in comparison to those developing the condition following cardiac surgery (Table 4-2). Those children with a medical cardiac condition all had a primary diagnosis of cardiomyopathy, a condition that can occur in any age group, unlike the majority of the children requiring surgery who as discussed above tend to require corrective congenital cardiac surgery within the first year of life. The mean weight of the children who develop a chylothorax was slightly higher than the median weight of the population (7.34 kgs vs. 4.8 kgs) (Table 4-2). This slightly higher mean reflected the greater age distribution and therefore weight of the children who presented with a primary medical cardiac condition, together with the older children who presented in the cardiac surgical and general surgical primary diagnostic groups.

Of the identically matched children within the BPSU and HES data no remarkable findings were made. The children's demographic characteristics reflected those of the main BPSU study group, as did the primary diagnostic groups. Indeed this sub-group of children were represented in each of the primary diagnostic groups (Table 4-62), with the majority, unsurprisingly, being in that of cardiac surgery (69.8%). The second most common diagnostic group was jointly a neonatal congenital and surgical (non-cardiac) link (Table 4-62) did differ from the total BPSU data and could suggest better reporting to HES rather than the BPSU, by neonatal units. The spread of children across the categories did however demonstrate a breadth of reporting across clinical specialities within England.

In the following sections, detailed data from the BPSU will be discussed and placed in the context of the research questions and previous literature.

5.4 Diagnosis of chylothorax

Clinicians most commonly confirmed the development of a chylothorax by laboratory verification of the triglyceride content of the pleural fluid ≥1.1mmol/litre, however there were variations and inconsistencies in diagnostic practices. Some centres did not obtain laboratory confirmation of triglyceride levels, lymphocyte predominance, total cell count or chylomicron presence in the pleural fluid, using clinical assessment and speed of accumulation as the diagnostic parameter, which could potentially lead to under-estimation of the incidence. Additionally, neonatal cases were often diagnosed on the basis of X-ray or ultrasound findings, without any biochemical pleural fluid analysis. Given that many of the children who develop a chylothorax are critically ill and have a generally poor level of nutrition at the time of clinical suspicion, it is important to clarify the effect of enteral nutrition on pleural fluid production and composition, otherwise a delay in diagnosis and treatment is possible.

No clinician identified requesting a Sudan 111 test to confirm diagnosis of a chylothorax and few clinicians requested biochemical analysis of the pleural fluid for chylomicron levels. It is of note that the former was identified over thirty years ago as the gold standard for diagnosing a chylothorax (Staat 1980) and in light of advances in clinical expertise and technology, its relevance in today's practice is questionable. Furthermore, there is no recent discussion within the literature of its use or relevance to current clinical practice. The low number of clinicians who reported requesting chylomicron levels to confirm the child's chylothorax was also of note, particularly when considering the definitive nature of this test in chylothorax diagnosis (Chan *et al.* 2005; McGrath 2010). However, this low number may link to there being no specific question relating to the use of chylomicron levels in diagnosing a chylothorax, within the study questionnaire. As such these results could be an underestimate of the number of cases confirmed in this way.

5.5 Treatment and management strategies

No national guidance exists to direct management strategies for these children and this is evident in the variety of reported treatments. An MCT diet and insertion of an intercostal pleural catheter were the most commonly reported strategies, followed by the administration of intravenous IV TPN and IV OCT or SST, all of which broadly follow the current available guidance (Cormack *et al.* 2004;Panthongviriyakul & Bines 2008). No specific characteristic linked the children receiving these latter intravenous therapies. They were cared for in differing hospitals and differing categories of hospitals. The children had a range of primary diagnostic presentations, were a range of ages and had differing discharge categories.

As suggested by Cormack *et al*. (2004) and Panthongviriyakul and Bines (2008), the majority of children appeared to have an MCT diet administered for between four to six weeks. Verification of the exact time period this treatment continued requires further investigation as, although the length of stay for many of these children was prolonged, a proportion of them were discharged to an alternative hospital, or home, prior to completing this MCT diet

treatment, therefore the exact date the diet ceased is unknown. The median number of days an intercostal pleural catheter remained in situ in this study (11 days) (Figure 4-4) reflected the median range reported in previous studies (6-15 days) (Allen *et al.* 1991;Biewer *et al.* 2010;Caserio *et al.* 2010;Chan *et al.* 2005;Shih *et al.* 2011), and although this study reported two outlying children who skewed these data, the majority required an intercostal pleural catheter for similar, or slightly fewer days (5-22 days) than the above studies (Section 2.7.1). When comparing this study's results with previous studies interpretation is problematic due to the small sample size of these latter studies, and although this study data could be interpreted as encouraging, the lengthy time intercostal pleural catheters were in situ remains a concern.

The use of multiple treatment strategies to manage these children was not uncommon and whilst the majority received two or three differing treatments some required five and six, with one child with a primary cardiac medical diagnosis was reported to have had seven differing treatments. This number of interventions is substantial and has considerable impact on the child and healthcare resources. With the lack of national guidance and research into optimal management strategies, multi-centre national controlled studies are required to establish the best treatment strategies and outcome for these children.

The exploratory analysis of the BPSU data identified a difference between the treatment category the child received and their corresponding weight (Table 4-20), suggesting lighter children are more likely to receive second and third line management strategies. This could possibly indicate that smaller, lighter children may be less tolerant of enteral feed, or their condition may be more acute, requiring more invasive IV or surgical management. The small number of cases in some of the categories made detailed analysis problematic. However, if categories had been collapsed further to increase cell numbers the data would have become less clinically relevant to health professionals caring for these children.

The difference between the child's primary diagnostic category and the treatment administered (Table 4-21) suggests that neonates are more likely to receive second and third line treatments, including IV medications and surgical interventions such as thoracentesis, pleurodesis or ligation of the thoracic duct, than children with a cardiac or non-cardiac primary diagnosis. This may again reflect the poor tolerance of younger children to oral or enteral diet and or their increased acuity of illness and need for IV therapy or surgical intervention.

It was encouraging to find general consensus across the UK in the strategies used to manage these children and to establish, in the absence of clear evidence on effective treatments, that conservative medical management precedes surgical intervention (thoracentesis, pleurodesis or ligation of thoracic duct). However there was widespread variation in the time these treatments continued, possibly reflecting both the lack of evidence on which to base practice and the variability in clinical response to various treatments between different children.

There are no reports of primary surgical intervention preceding medical management for chylothorax treatment in children. Data are therefore not available to compare how the risks, cost and extended time period spent in hospital receiving medical management, compares with that of primary surgical management.

With no national protocol existing to direct clinicians in their management of these children, it was not surprising to discover that treatment was based on clinician preference or locally developed guidance.

5.6 Interventional procedures undertaken prior to the chylothorax developing

Whilst it was evident that the majority of children had been diagnosed with a chylothorax following an interventional procedure, the questions asked in this study did not elicit whether any child had a chylothorax prior to any intervention. This would be an area that would require further investigation in future studies.

5.7 Care setting and SHAs caring for these children

The majority of children who developed a chylothorax were cared for within tertiary cardiac hospitals, with SHAs 5 and 7 caring for the highest number of children and SHAs 8 and 13, the lowest (Table 4-11). With most of these children developing a chylothorax following cardiac surgery, this information provides some assurance that care for these children is being appropriately undertaken in centralised paediatric cardiac surgical centres within the UK. Although only the PICANet data confirms a stay in intensive care, with tertiary cardiac hospitals reporting the majority of the cases, this supports the literature reporting these children are most commonly initially managed in an intensive care environment. There was no apparent connection between the hospital, age or underlying diagnosis of those children who were cared for in DGHs rather than tertiary centres (Table 4-11). The reporting of children receiving such complex care being managed in DGHs is of concern and may reflect the varied case mix of the children, however the reasons behind and rationale for this care in non-specialist environments requires further investigation.

There was no significant difference between the treatment category, length of stay, or survival for different categories of hospital. This is most likely related to the small number of children cared for in DGHs although alternative explanations are possible. Additional data and more in-depth analysis are required before further substantive conclusions are drawn.

5.8 Length of child's hospital stay and their discharge destination or outcome

The prolonged hospital stay these children are commonly subjected to poses considerable risk. It exposes them to an increased likelihood of hospital acquired infections, nutritional compromise and regression, with their families or carers often experiencing substantial levels of stress (Beghetti *et al.* 2000;Rennick & Rashotte 2009). With many of these children having multiple clinical complex needs (Doerr *et al.* 2005;Soto-Martinez & Massie 2009), it is not possible to attribute their prolonged length of stay solely to the chylothorax development, as severity of illness may drive the length of child's stay. However, with many of the treatment options continuing for extended periods of time a link between the two has to be considered.

The paucity of evidence in this area has meant there are no other discharge data available to use as a comparison against the children in this study. Whilst the majority of children survived their hospital admission and were discharged home, a moderate proportion (17%) (Table 4-18) were still receiving treatment at the time the data were collected, hence these datasets were curtailed and the children's outcome was unknown. Greater consideration regarding how to manage the longer term collection of data relating to these children should perhaps have been given at the start of the study. However, the prolonged length of treatment some of these children required was not anticipated. A follow-up study to establish this information would provide a more complete picture of the children's disease progression. It might also allow information to be collected on the medium term impact on the child and family of having an unexpected complication and prolonged intensive care stay. However, this would require an appropriately designed study which could include a longitudinal follow-up survey, individual case-series, or a qualitative study such as phenomenology.

Even for those children discharged home in the study period, their stay tended to be lengthy, which in a challenging economic climate where all healthcare costs need to be optimised, requires further attention. Improving care from

the onset and supporting the family towards earlier discharge may help reduce hospital length of stay significantly.

The significance of the relationship between treatment category and the child's length of stay (Table 4-29) may suggest that children requiring specific management strategies potentially have a chylothorax which is more difficult to resolve, hence requiring a prolonged stay in hospital. Alternative interpretation could be that the more invasive the treatment the longer the child's length of stay. This appears to relate to those children receiving second and third line treatments which include IV drug therapies, parenteral feeding and surgical intervention, all of which are invasive practices and as an acute management strategy require administration in a hospital environment.

The significant difference between the child's survival and the different treatment categories (Table 4-30) is likely to reflect the fact that a substantial proportion of children who receive third line treatment do not survive. This could indicate vulnerability in the group receiving surgical intervention for chylothorax, which may be associated with a worse outcome. This observation is supported by the logistical analysis which shows, when compared to the reference group of first line treatment (Table 4-31), those children who received second and third line treatments had an increased likelihood of being in the non-survival group.

The positive correlations that exists between the child's age and weight and days of treatment (Table 4-22) suggests older children required more days of treatment to gain chylothorax resolution, possibly indicating this group of children are more difficult to treat. However, the negative correlation between the child's age and weight and length of their hospital stay (Table 4-22) suggests an overall shorter length of time older children remain in hospital. These correlations may also suggest that younger children gain earlier chylothorax resolution due to the lower number of treatment days. However, it is possible these results reflect an increased severity of illness and vulnerability in this group, where a shorter hospital stay is an indicator of younger children

not surviving to discharge, although the exploratory analysis undertaken in Table 4-23 indicates no significant difference between the child's weight and their survival. This result is however reversed in the logistical analysis where there is a greater probability of children being in the non-survival group as they get older (Table 4-31). Nonetheless, with the majority of these correlations only showing a weak relationship drawing any meaningful conclusion is problematic.

No substantial data on mortality had been published on children who developed a chylothorax. Whilst studies did report on the children who did not survive in their cohort or case-series studies, the sample numbers were small. The reported mortality for this study of children with chylothorax was 12.5% in the total population, with 50% of these requiring cardiac surgery, and within the cardiac surgical sub-group, the mortality was 9.5%. Although the mortality rates for specific cardiac surgical procedures are available for individual centres within the UK (NICOR 2013), with the small number of children in this study, the differing surgical procedures undertaken and the variety in the terminology used to report the cases, comparison of mortality data would be limited and have little value. Furthermore, to substantiate the above mortality statistics establishing the discharge destination or outcome of the 29 children (Table 4-18) that were still receiving treatment at the time of data collection is also required. Of additional note however, was the logistical analysis that identified an increased probability of girls being in the non-survival group as were all children as they got older (Table 4-31). The relevance of these finding requires further analysis.

The hospital discharge destination or outcome of the children reported by HES was more positive than that reported by the BPSU, the former with a mortality of 6% in comparison to the BPSU data which showed 12.5%. This reduced mortality within the HES data is consistent with data that contains both prevalence and incidence cases. Furthermore, with the BPSU population solely including incidence cases this could potentially indicate more acutely unwell children who may be more likely to die, whereas the prevalence of cases

included in the HES population may include less sick children receiving on-going care.

5.9 Cardiac surgical children

The highest incidence of children in this study developing a chylothorax were those requiring an open cardiac surgical procedure classified in RACHS-1 Categories 2 and 3 (Table 4-36), with a considerable number of children requiring either a Fontan procedure or Tetralogy of Fallot repair, which could suggest that high systemic venous pressures may have an effect on chylothorax development following cardiac surgery as much as direct thoracic duct damage. These data provide robust support to the existing limited evidence reporting on procedures most linked to chylothorax (Chan *et al.* 2005;Milonakis *et al.* 2009;Nguyen *et al.* 1995). This study further identified a considerable proportion of children who developed a chylothorax following cardiac surgery also had a congenital disorder (Table 4-34), with children who had Down syndrome in combination with an atrio-ventricular septal defect being most commonly reported (Section 4.1.12.3), although no previous study specifically highlights this. This finding requires further scrutiny as it may inform how parents and children are advised regarding expectations in the post-operative period. No child who developed a chylothorax following cardiac surgery had a procedure in RACHS-1 Category 5. This is likely to be reflective of the Category containing only two procedures (Appendix 7), both of which are required for particularly rare congenital cardiac conditions (NICOR 2013).

Children falling into RACHS-1 Categories 2 and 3 receive interventions common to all paediatric tertiary cardiac centres in the UK (NICOR 2013), whereas those children requiring procedures in Category 6 are only operated on in a limited number of these centres. Mery *et al.* (2013) reports chylothorax being most commonly linked with increased cardiac procedural complexity, with RACHS-1 Categories 5 and 6 having the highest incidence of chylothorax occurrence in their study at 5.2%. This was not a result that was reflected in this study, where RACHS-1 Categories 2 and 3 had a substantially higher

number of children who developed a chylothorax (Table 4-36). This may relate to the large sample size and eight-year time frame of Mery *et al's* (2013) study, however further analysis of these data will be required once the full data is published.

With many of the children in the BPSU study population having a primary diagnostic category of cardiac surgery, it was not surprising that the majority of findings from this group were similar to those of the children as a whole. The one analysis of significant difference however was the logistical analysis that identified children who remained in hospital for 21-50 days had an increased probability of survival when compared to the reference group of 4-10 days (Table 4-51). This could indicate the vulnerability and increased clinical acuity of children in the initial days of treatment following cardiac surgery and development of a chylothorax, and as days progress the child's condition improves, as does the likelihood of their survival. . Alternatively however, as stated above, it could reflect the increased severity of illness in these children, where a shorter hospital stay is an indicator of younger children dying earlier.

5.10 Limitations of the study

5.10.1 Selection bias

The study protocol aimed to minimise selection bias and optimise ascertainment by accessing data from four data sources. The study applied a triangulation methodology to gain assurance that the dataset provided by the BPSU was the entire population of children who developed a chylothorax in the UK within the study period.

Whilst the four data sources were accessed, the minimal identifiable information provided by CCAD and PICANet together with the small number of cases reported by these two data sources, provided no added assurance of BPSU data completeness. The provision of more patient identifiers by CCAD

and PICANet would have allowed for greater matching of cases to the BPSU data and the increased accuracy in the overall population.

The lack of co-morbidity data provided by HES was unforeseen and whilst data were requested on any child who had one of five chapter codes recorded within their primary or secondary code or co-morbidity coding, these were not differentiated in the data provided to the investigator. However, following discussion with HES clarification was obtained that the requested codes were all present in each child's admission episode. The difference in the number of children reported by HES as developing a chylothorax in the study period, in comparison to those obtained via the BPSU was likely to relate to the former dataset including both prevalence and incidence cases, rather than solely incidence, and the request for data on five chapter codes, rather than limiting the application to the two codes most likely to have represented chylothorax development. Despite this, consideration should be given to the completeness of the BPSU dataset. With this knowledge and knowing that a few children who developed a chylothorax were not reported via the BPSU, the researcher acknowledges the study has been on a sample of children who developed a chylothorax in the UK, rather than the complete population.

5.10.2 BPSU methodology

The limitations to the BPSU methodology were identified in Section 5.2.1.

5.10.3 Coding issues

A common and reasonable criticism of health service research that uses hospital coding in data collection is the potential for coding error. There is a considerable body of literature addressing the rate of such errors (Section 3.5.8.1) (O'Malley *et al.* 2005;Shah *et al.* 2011;Westaby *et al.* 2007), which indicates that inaccuracy may be quite high for certain conditions. The literature specifically indicates that there is a greater reliability of chapter level coding (Stausberg *et al.* 2008) than individual chapter codes, the latter being those requested for this study. Although it was necessary to access these

more specific codes to gain the data on chylothorax cases, it is probable that errors are likely to be present.

5.10.4 Questionnaire limitations

Every effort was made to reduce questionnaire bias and ensure a high level of face and content validity (discussed in Section 3.5.6.6). This mainly proved successful based on the effective completion of the questionnaire and limited additional free text information clinicians felt necessary to provide. However the lack of questions requesting specific information on the use of the Sudan 111 test, or chylomicron analysis of pleural fluid to confirm a chylothorax was an oversight. Although these tests were discussed within the literature (Staat 1980; Chan *et al.* 2005; McGrath 2010), their omission was not raised as a concern during the pilot phase. Some clinicians did provide additional information relating to the management of the child although the data completeness relating to the use of these tests within this population is unknown. The data that were collected however does provide robust useful information regarding the diagnostic tests used to confirm a chylothorax in children in the UK.

5.11 Chapter summary

The main aim of this study was to establish the current incidence and describe the patient profile of children who developed a chylothorax in the UK, with secondary aims being to describe the clinical management strategies prescribed and administered to treat these children, together with establishing information regarding their discharge destination or outcome. Having analysed information from all the datasets it is evident that the condition is rare and for the first time a national incidence can be reported. The reported link between chylothorax and cardiac surgery has been supported by this study with the finding of a similar incidence (Section 2.4). Additional verification that a link exists within the neonatal and neonatal congenital population has also been made.

Robust data have been provided on the young age of those children who are affected by chylothorax and greater clarity is now available on the investigations and strategies clinicians use to diagnose the condition. In the UK, whilst there is some consistency in the management strategies prescribed and administered to treat these children with an MCT diet, intercostal pleural catheter, IV TPN and IV OCT/SST being the most commonly applied, no national guidance exists and further treatments vary considerably, resulting in inconsistencies in the quality of care children receive. Whilst these therapies are all reported within the literature, this study provides the first evidence that these are applied on a national scale, although inconsistently across centres.

With robust data now being available on the prolonged length of stay these children experience, powerful evidence has been provided on the need to undertake further research to improve their clinical care, reduce their hospital stay and the demand on clinical resources.

6. Conclusions

6.1 Contribution to existing knowledge

This is the first national multi-centre study of chylothorax in children. It identifies with greater accuracy than previously available, the UK incidence of chylothorax in children, together with the incidence following cardiac surgery. It is these children who are reported as being of the highest risk of developing this condition, followed by neonates. Evidence is provided on the discrepancies in clinical data submission for this condition to both the CCAD and PICANet National Audit Databases and discusses the challenges that arose around identifying chylothorax cases in children within the HES data.

Robust evidence is provided demonstrating that a MCT diet and intercostal pleural catheter are the most frequently prescribed management strategies, although up to seven differing treatments can be administered with a median of two being received by the majority of children, thus emphasising the potential resource implications for hospitals' caring for children who develop a chylothorax. This study clarifies the length of hospital stay and discharge destination or outcome for these children, together with the mortality linked to this condition.

6.2 Implications of the study

One of the main findings of this study is identification of the incidence of chylothorax in children in the UK and recognition nationally and internationally of the number of children who develop the condition following cardiac surgery. This information is of particular relevance for medical and nursing personnel who discuss post-operative co-morbidities with families and carers of infants requiring cardiac surgery. Providing these families with accurate factual information regarding realistic expectations, possible complications and the risks associated with surgery is vital to ensure informed consent is obtained and families are adequately and appropriately prepared.

Although this incidence is of particular relevance to the UK, it also provides primary new data for healthcare professionals internationally. Whilst previous literature has reported chylothorax development following cardiac surgery the evidence has been based on poor quality, small scale retrospective cohort studies and case-series. This study is the first to provide robust data that supports these findings.

Over half of the children in this study remained in hospital for 11-40 days which reflected the prolonged hospital-based management strategies these children required to treat their condition. This prolonged period of in-patient hospital care has substantial implications not only for the child who is put at greater risk of developing nosocomial infections, but also for the families who may not be in their local hospital, may be separated from other siblings and partners and may have had to take extended time away from work with financial implications. Additionally, the institutions are affected regarding increased financial costs required to treat these children and the impact this resultant reduced hospital bed capacity has on the ability to admit and treat other children. This information provides compelling evidence to substantiate the need for further research to be undertaken, particularly associated with the management strategies prescribed and administered to treat these children and the need to investigate providing this care more locally to the child's home. The data also allow better information to guide parents on probable minimal length of treatment if their child develops a chylothorax and the possible protracted length of hospital stay, which can frequently taking several weeks.

The high mortality both within the entire group (12.5%) and the cardiac surgical sub-group (9.5%) again provide primary new data in this area. This information is of key importance for medical and nursing staff caring for these children as it will allow for accurate, evidence-based information to be shared with these families, as well as providing a baseline from which further research focusing on morbidity can be developed.

A further implication from this study was the identification of a gap in the ICD-10 coding system. There is a need for greater clarification and direction on the documentation of co-morbidities in neonates and children, as well as improved education on the specific coding for chylothorax. Whilst there is a designated chapter code for chylothorax (J94.0), there was evidence that this was not consistently applied to those children who developed the condition, and where documentation was present, a variety of codes were applied. Improved coding would provide more robust data to hospitals and Health Commissioners and is particularly pertinent given the Payment by Results system and the suggestion that ill-defined conditions are hidden costs that could exceed that of primary admission diagnoses (Spencer & Davies 2012). This calls for further research into the documentation and clarification of paediatric co-morbidities.

6.3 Recommendation for practice and further research

This study has demonstrated further that it is possible to collect national surveillance data on a rare childhood disorder with an assumed low incidence. However data completeness may be difficult to achieve. The results provide the basis for further research in this area that would provide the evidence required to plan and implement effective and targeted care, in order to improve outcome.

Initially, the retrospective collection of the discharge destination or outcome data of those children who were still receiving treatment when the study data were collected would allow precise confirmation of the reported mortality statistics. Additionally, a follow-up study of all children who participated in the primary research project would provide further in-depth information regarding the recovery and progress of these individual.

Undertaking further research that would establish the individual hospital incidence of chylothorax development in the two most common diagnostic categories of cardiac surgical and neonatal children, together with mapping

their hospital management strategies would provide informative data to help direct future treatment strategies.

As a result of the varied and multiple management strategies prescribed and administered to treat these children, it would be prudent to conduct a multi-centre study focusing on this area of care. With the knowledge that the majority of children develop a chylothorax following cardiac surgery and with the centralisation of children's cardiac services in the UK, it would be beneficial to focus studies in this specific clinical speciality. These could include case controlled studies focusing on causation, randomised controlled studies examining treatment effects and analysing the RACHS-1 categories the children are assigned to. Similar studies could also be undertaken in neonates who developed chylothorax which would also provide helpful information to improve their management and could be investigation individually or as a comparative group to the above. All studies may need to be international in order to achieve an adequate sample size. To prevent the parental refusal challenges Cannizzario *et al.* (2006) encountered when they commenced a randomised, double blind, placebo, controlled study of SST with a placebo alternative, designing comparative studies between known, standard effective treatment options would be valuable.

Investigating the long term outcome of these children as an entire cohort, together with an analysis of the differing treatment strategies they received, would also provide insightful information for future management of these children.

With this study demonstrating discrepancies within the data provided by two key UK databases, CCAD and PICANet, further research is needed to establish the accuracy of these findings and to determine whether processes could be implemented to improve them, both individual or jointly. Establishing more robust systems within these databases to report other complications, secondary conditions and co-morbidities would provide valuable additional information to help optimise the care for these children.

Similarly, the challenges experienced with the HES data regarding the availability of differing coding possibilities for the same condition requires further investigation. Understanding if this is a common problem, when and how it occurs and if it could be addressed would assist in the interpretation of HES data and its use in future studies.

The above suggestions for further research focus on a quantitative methodology, however additional qualitative research within this area should be considered. With the majority of children who develop this condition being ≤12 months, undertaking studies with parents whose child develops a chylothorax and understanding their experience would be valuable, as would considering studies with older children. For the children, gaining insight into their experiences of having this condition, understanding what it is like to remain in hospital, possibly in intensive care for prolonged periods of time, being exposed to differing treatment strategies and differing sights and sounds of hospital environments would add valuable information to this subject area. This would also be important in managing treatment, information giving and supportive care for families during the entire episode, from pre-operative to convalescent stages. Given the age of the majority of the children this might however necessitate an international study to achieve an adequate sample.

Finally, once research studies have been undertaken and results obtained on the effectiveness of differing treatment strategies, the development of national guidance to direct clinicians in the optimal management for these children is essential.

Of additional importance is dissemination of the results of this study to medical, nursing and allied health professionals who care for these children, together with their parents. This dissemination is required locally, nationally and internationally, through clinical care and discussion, journal papers and conference presentations and is a process that has already commenced. The

dissemination of this information through my Consultant Nurse role is assisted by my involvement and leadership in the clinical care of these children locally and nationally, the decision-making knowledge and expertise I have developed within the role, the practice and service development remit of the post and the commitment I have to embed evidence in clinical practice.

6.4 Concluding remarks

The development of a chylothorax in children in the UK is not common. The majority of cases occur in infants, with a national incidence of 14 in 100,000 (0.0014%) and this study confirms that there is a notable link with the development of a chylothorax following cardiac surgery. It further identifies that children with Down syndrome in combination with an atrio-ventricular septal defect or ventricular septal defect are at an increased likelihood of developing the condition.

Children are cared for in a substantial number of tertiary and district general hospitals across the UK and the length of stay for these individuals is prolonged and therefore the impact on the child, their family and hospital resources is significant. The reported mortality is high and obtaining any national comparative group data has not been possible.

With the majority of children developing the condition following cardiac surgery there may be a need to re-consideration whether chylothorax development is a surgical complication and in many cases iatrogenic, particularly when noting the variation in the number of reported cases across tertiary cardiac centres.

Whilst there are common strategies regarding how the diagnosis is made and the treatment methods applied, the study identifies that national guidance within this clinical area requires development and further studies are needed to confirm the efficacy of the various treatment options.

Appendices

Appendix 1 – Search Strategy – All Databases

Search Number	Database	Search Term(s)	Number of Papers
1	AMED	Chyl*.ti,ab	11
2	AMED	Chylothorax.ti,ab	4
3	AMED	(pediatric OR paediatric* OR child* OR infant*).ti,ab	16242
4	AMED	1 and 2 and 3	0
5	BNI	Chyl*.ti,ab	6
6	BNI	Chylothorax.ti,ab	6
7	BNI	(pediatric OR paediatric* OR child* OR infant*).ti,ab	21025
8	BNI	1 and 2 and 3	0
9	CINAHL	Chyl*.ti,ab	344
10	CINAHL	Chylothorax.ti,ab	141
11	CINAHL	(pediatric OR paediatric* OR child* OR infant*).ti,ab	207341
12	CINAHL	1 and 2 and 3	33
13	EMBASE	Chyl*.ti,ab	10045
14	EMBASE	Chylothorax.ti,ab	2704
15	EMBASE	(pediatric OR paediatric* OR child* OR infant*).ti,ab	1421589
16	EMBASE	1 and 2 and 3	507
17	HEALTH BUSINESS ELITE	Chyl*.ti,ab	7
18	HEALTH BUSINESS ELITE	Chylothorax.ti,ab	0

Appendix 1

Search Number	Database	Search Term(s)	Number of Papers
19	HEALTH BUSINESS ELITE	(pediatric OR paediatric* OR child* OR infant*).ti,ab	67946
20	HEALTH BUSINESS ELITE	17 and 18 and 19	0
21	HMIC	Chyl*.ti,ab	0
22	HMIC	Chylothorax.ti,ab	0
23	HMIC	(pediatric OR paediatric* OR child* OR infant*).ti,ab	29811
24	HMIC	21 and 22 and 23	0
25	MEDLINE	Chyl*.ti,ab	9140
26	MEDLINE	Chylothorax.ti,ab	2352
27	MEDLINE	(pediatric OR paediatric* OR child* OR infant*).ti,ab	1207600
28	MEDLINE	25 and 26 and 27	393
29	PsycINFO	Chyl*.ti,ab	45
30	PsycINFO	Chylothorax.ti,ab	2
31	PsycINFO	(pediatric OR paediatric* OR child* OR infant*).ti,ab	529574
32	PsycINFO	29 and 30 and 31	0

Appendix 2 – Search Strategy Applied to MEDLINE, CINAHL, BNI and EMBASE

Search Number	Database	Search Term(s)	Number of Papers
1	MEDLINE	exp CHYLOTHORAX/	2365
2	MEDLINE	exp PLEURAL EFFUSION/	15464
3	MEDLINE	LYMPHANGIOLEIOMYOMATOSIS/	790
4	MEDLINE	CHYLOUS ASCITES/ OR CHYLE/	2070
5	MEDLINE	THORACIC DUCT/	3649
6	MEDLINE	exp LYMPHATIC DISEASES/	323362
7	MEDLINE	LYMPHATIC ABNORMALITIES/ OR LYMPHANGIOMA, CYSTIC/ OR LYMPHATIC SYSTEM/ OR LYMPHANGIOMA/	14904
8	MEDLINE	exp SOMATOSTATIN/	17186
9	MEDLINE	OCTREOTIDE/	6038
10	MEDLINE	Chyl*.ti,ab	9140
11	MEDLINE	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	381577
12	MEDLINE	11 [Limit to: Publication Year 1990-Current]	217266
13	MEDLINE	12 [Limit to: Publication Year 1990-Current and (Age Groups All Child 0 to 18 years)]	49553
14	MEDLINE	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	375626
15	MEDLINE	1 and 14	1337
16	MEDLINE	15 [Limit to: Publication Year 1990-Current]	829
17	MEDLINE	16 [Limit to: Publication Year 1990-Current and (Age Groups All Child 0 to 18 years)]	282

Appendix 2

Search Number	Database	Search Term(s)	Number of Papers
18	MEDLINE	10 and 14 [Limit to: Publication Year 1990-Current and (Age Groups All Child 0 to 18 years)]	502
19	MEDLINE	10 and 14	3312
20	MEDLINE	19 [Limit to: Publication Year 1990-Current]	1916
21	MEDLINE	20 [Limit to: Publication Year 1990-Current and (Age Groups All Child 0 to 18 years)]	502
22	MEDLINE	1 [Limit to: Publication Year 1990-Current and (Age Groups All Child 0 to 18 years)]	464
23	MEDLINE	1 or 4 [Limit to: Publication Year 1990-Current and (Age Groups All Child 0 to 18 years)]	620
24	MEDLINE	4 or 10 [Limit to: Publication Year 1990-Current and (Age Groups All Child 0 to 18 years)]	1022
25	MEDLINE	1 or 4 or 10 [Limit to: Publication Year 1990-Current and (Age Groups All Child 0 to 18 years)]	1065
26	MEDLINE	Duplicate filtered: [1 [Limit to: Publication Year 1990-Current and (Age Groups All Child 0 to 18 years)]]	462 Unique results 2 Duplicate results

Appendix 3 – BPSU Surveillance System

2 How the Surveillance System Works

Selection of studies for inclusion in the scheme

A study is eligible for participation in the scheme if the subject is a rare childhood disorder (or rare complication of a commoner disease) of such low incidence as to require cases to be ascertained nationally in order to generate sufficient numbers for study.

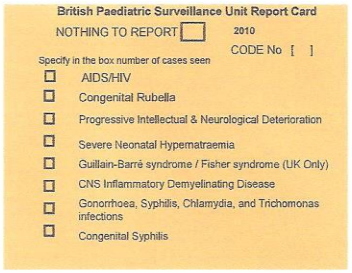
The number of conditions under surveillance is usually limited to 12. The BPSU application procedure consists of two phases: a screening phase based on an outline of the study and a detailed consideration of the full application. Details about the BPSU application procedure can be downloaded from the website at http://www.bpsu.inopsu.com.

Factors that increase the likelihood of a study being accepted include scientific importance, clear objectives, a workable case definition and proposals with outcomes of clear importance to public health. Once approved by the BPSU Executive, studies require approval from the Research Ethics Committee (REC) and Ethics and Confidentiality Committee of the National Information Governance Board before commencement.

The reporting system

Those participating in the reporting system include consultant paediatricians who are either members of the RCPCH or the Faculty of Paediatrics of the Royal College of Physicians of Ireland.

Surveillance is 'active' in that the BPSU office actively sends out cards to clinicians asking for cases to be reported on the BPSU orange card (Figure 1). Each month, all clinicians participating in the surveillance scheme are sent the orange card listing the conditions currently under surveillance; follow-up reminders are sent to those who have not returned their card after two months. A set of instructions for completing the card, including case definition of the conditions listed on the card is also circulated. When a new study begins, the mailing also includes a specially produced study protocol card and other information about the study.


British Paediatric Surveillance Unit Report Card

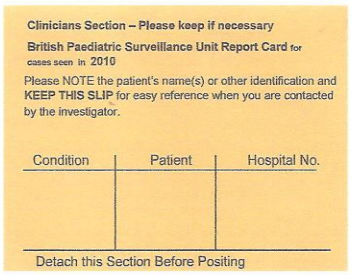
NOTHING TO REPORT ☐ 2010

CODE No [ ]

Specify in the box number of cases seen

- ☐ AIDS/HIV
- ☐ Congenital Rubella
- ☐ Progressive Intellectual & Neurological Deterioration
- ☐ Severe Neonatal Hypernatraemia
- ☐ Guillain-Barré syndrome / Fisher syndrome (UK Only)
- ☐ CNS Inflammatory Demyelinating Disease
- ☐ Gonorrhoea, Syphilis, Chlamydia, and Trichomonas infections
- ☐ Congenital Syphilis

Figure 1: Orange Card Side A


Clinicians Section – Please keep if necessary

British Paediatric Surveillance Unit Report Card for cases seen in 2010

Please NOTE the patient's name(s) or other identification and KEEP THIS SLIP for easy reference when you are contacted by the investigator.

Condition	Patient	Hospital No.

Detach this Section Before Positing

Figure 2: Orange Card Side B

When reporting a case, respondents are also asked to make a note of the case (Figure 2) and **keep** the details for future reference as they will later be contacted by the study team with a questionnaire about each case.

Participants are also expected to return cards **even if they have no cases to report** - there is a 'nothing to report' box on the card for them to tick. This is an important feature of the surveillance scheme as it allows us to measure compliance to the reporting system. The compliance rates are thus continually monitored ensuring good coverage of the paediatric surveillance scheme across the whole of the UK and Ireland.

Follow-up and confirmation of case reports

On receiving a case report the BPSU informs the relevant study team. To gather further information the study team sends a short questionnaire to the reporting clinician. Particular care is taken

to ensure that questionnaires are as short as possible, clear, straightforward and not excessive in their demands. As the questionnaire cannot be fully anonymised, the amount of patient identifiable data collected is strictly limited to preserve patient confidentiality. The study investigators report back to the BPSU, indicating when cases have been confirmed or are duplicate case reports (Figure 3). Duplication of reporting is most likely to occur when the condition requires referral to another clinician, but this is encouraged, as it is better to receive duplicate reports than to miss a case.

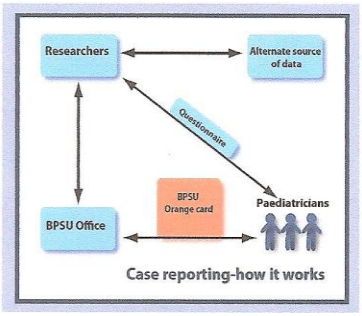


Figure 3: Surveillance mechanism

Table 2 (page 10) shows the number of cases reported to the BPSU from its inception until the end of 2010 for conditions under surveillance at December 2010. The extent to which investigators receive survey data, identifying incorrect reports and duplicates and the speed in which this is done is known as the **'completion rate'**. The number of cases which have so far been subsequently confirmed as meeting the case definition are also shown.

The time taken to follow-up a case report varies greatly between conditions and may be longer if microbiological or pathological details are required to confirm a case. The completion rate is high. For example, as of May 2011, only 834 (7%) of the 13012 case reports had yet to be followed-up. The final completion rate normally averages between 90-95% for a study undertaken through the BPSU.

Table 3 (page 11) summarises the outcome of the follow-up of all cases reported to the BPSU by the end of year 2010 and provides evidence for the level of accuracy of reporting by participating clinicians.

To improve case ascertainment for specific studies where a child may see specialist clinicians, consultants working in a number of other specialties have been invited to participate in the scheme. Pathologists have been included in the BPSU reporting scheme since 1992 and most studies of paediatric infections involve laboratory reporting by microbiologists. Paediatric surgeons (intussusception) and burns specialists (toxic shock syndrome) have recently been included in the reporting system. Apart from helping to improve ascertainment such complementary data sources help to validate the surveillance system.

Funding

The BPSU continues to be in receipt of a grant from the Department of Health to cover the majority of the running costs of the unit. In addition, the BPSU asks surveillance teams to contribute a sum to cover specific administrative costs. These funds also permit us to undertake additional activities such as holding workshops to support current and potential investigators and conferences. The BPSU is also grateful for the ongoing support that it receives from the Royal College of Paediatrics and Child Health, the University College London - Institute of Child Health and the Health Protection Agency.

Sir Peter Tizard Bursary

The bursary, named after one of the founders of the BPSU, is offered as a competitive award. With a value of upto to £15,000 it offers, each year, the opportunity for a junior doctor or newly appointed consultants to use the facilities to undertake their own surveillance study and to learn more about disease epidemiology. To date seven awards have been made. Details of the bursary are available on the BPSU website at www.bpsu.inopsu.com.

Appendix 4 – Patient Information Leaflet

BRITISH PAEDIATRIC SURVEILLANCE UNIT

WHAT IS THE BRITISH PAEDIATRIC SURVEILLANCE UNIT (BPSU)?
The aim of the BPSU is to encourage the study of rare conditions in children. It was founded in 1986 by the Royal College of Paediatrics and Child Health, the Health Protection Agency and the Institute of Child Health (London).

WHAT DOES THE BPSU DO?
It allows doctors and researchers to find out how many children in the UK and the Republic of Ireland are affected by the particular disease or condition each year - this is called epidemiological surveillance. Doctors can also gather information about all the cases of a particular rare condition so they can begin to understand what might have caused it and how to diagnose and treat.

On receiving the card, the BPSU informs the investigation team, who send the reporting doctor a short confidential questionnaire for more information about the affected child. BPSU researchers never contact families or children and surveillance studies don't ever affect a child's treatment. The purpose is ONLY to collect information to learn more about the condition.

HOW DOES THE BPSU WORK?
Each month the unit sends a distinctive orange card to over 2400 consultant paediatricians; the card lists the rare conditions currently being studied.
If a doctor has seen a child affected by one of these conditions they tick a box on the card and return it to BPSU.

WHAT HAS THE BPSU ACHIEVED?
PUBLIC HEALTH IMPACT
The BPSU has now helped to undertake surveys of over 60 rare conditions which may affect children. These have helped to increase understanding of why the conditions occur and can help to provide better diagnoses and treatments.

(From the BPSU Public Information Leaflet –' Investigating rare childhood conditions for the future health of the nation')

For further information contact:
British Paediatric Surveillance Unit
Royal College of Paediatrics & Child Health
5-11 Theobalds Road, London WC1X 8SH
Tel: +44 (0) 207 0926173 / 74
E-Mail: bpsu@rcpch.ac.uk
Website: http://bpsu.inopsu.com

University Hospitals Bristol NHS
NHS Foundation Trust

BRITISH PAEDIATRIC SURVEILLANCE UNIT

PUBLIC INFORMATION SHEET

CHYLOTHORAX STUDY IN INFANTS AND CHILDREN

TOWARDS BETTER TREATMENT AND MANAGEMENT OF INFANTS AND CHILDREN WHO DEVELOP A CHYLOTHORAX

WHAT IS A CHYLOTHORAX ?

A **chylothorax** is a condition that results in a build-up of fluid in the space around the lungs. The fluid, called chyle, is a normal fluid that is made when the body digests fat and is usually transported in lymph vessels. If this fluid builds up around the lungs it puts pressure on them and makes breathing more difficult.

WHY DOES A CHYLOTHORAX DEVELOP ?

Sometimes the vessels that transport the chyle become damaged and leak and then the fluid builds up around the lungs. The most common causes for a chylothorax to develop include:

- a congenital cause
- trauma caused by thoracic surgery
- lymphoma (cancer of the lymph system)

Appendix 4

The Chylothorax Study

The treatment and management of infants and children with a chylothorax is varied and it is currently difficult to know how best to manage children with this condition.

A study has been designed to gain information about infants and children who develop a chylothorax with the aim of improving understanding of the condition and how best to treat it.

The British Paediatric Surveillance Unit (BPSU) is supporting this study (see back page of leaflet), as well as the Paediatric Intensive Care Society (PICS) and the British Congenital Cardiac Association (BCCA) and we hope this information leaflet provides you with the necessary information about the study.

Where Is This Study Happening

The study is being led by medical and nursing staff at Bristol Royal Hospital for Children and will be taking place in all hospitals across the United Kingdom, Northern Ireland and the Channel Islands.

How Long Will The Study Go On For?

The study will continue for 13 months.

How Will The Information Be Collected ?

The medical doctors caring for children who develop a chylothorax will fill in a questionnaire and send this anonymous information to the study investigators in Bristol.

Through analysing this information we hope to Increase understand of the development of a chylothorax and improve treatment.

What Are The Possible Risks and Benefits

Information collected will not identify any individual and confidentiality will be maintained at all times.

By collecting the information about infants and children who develop a chylothorax it is hoped to increase understanding of the condition and help improve treatment for individual.

Who Should Be Contacted If You Have Any Questions About This Study?

Please contact the British Paediatric Surveillance Unit of the Royal College of Paediatrics and Child Health, London (see over page).

Appendix 5 – Capture-recapture

Statistical formulae for two-source capture-recapture analysis (Hook & Regal 1995).

		Source Y	
		Yes	No
Source Z	Yes	a	b
	No	c	x

$$N = a + b + c + x$$

b – Source 1 c – Source 2 a – Population common to both sources.

Estimated values	Maximum likelihood estimator (MLE)	Nearly unbiased estimator (NUE)
x - unobserved cell / population	bc/a	bc/(a+1)
N - Total population	a+b+c+(bc/a)	a+b+c+(bc/(a+1))

Appendix 6 – Questionnaire

University Hospitals Bristol NHS
NHS Foundation Trust

BPSU ID:

British Paediatric Surveillance Unit Study

Chylothorax in Infants and Children

Data Collection Form

Reporting Instructions:
Please see BPSU flyer for reporting instructions

Please return the completed form to:

Ms Caroline Haines, Nurse Consultant PIC/PHDU
C/o PICU, Level 4, Bristol Royal Hospital for Children
Upper Maudlin Street, Bristol BS2 8BJ

Phone: 0117 342 8380 / Fax: 0117 342 8910
Email: Caroline.Haines@UHBristol.nhs.uk

Referring Hospital: _____

Consultant Responsible for Reporting Case: _____

Person Completing Questionnaire: _____

Email Contact Address: _____

Contact Telephone Number: _____

Date Form Completed: _____

Section 1: Child's Details

1.1 Child's NHS Number or Equivalent: ☐☐ ☐☐☐☐ ☐☐☐☐

1.2 Postcode (first part only): ☐☐☐☐

1.3.1 Date of Birth (MM / YY): ☐☐ / ☐☐

1.3.2 Gestational age at birth if <1 yr _____ wks + _____ days

1.4 Gender (please tick) ☐ Male ☐ Female

1.5.1 Child's current weight (kg): _____ kgs

1.5.2 Child's birth weight (kg): (if < 1 yr): _____ kgs

1.6 Date diagnosis made (DD / MM / YY): ☐☐ / ☐☐ / ☐☐

1.7 Child's Ethnicity (Please tick)

☐ WHITE
☐ CHINESE
☐ NOT KNOWN
☐ ASIAN or ASIAN BRITISH
☐ MIXED
☐ BLACK or BLACK BRITISH
☐ OTHER

1.

Appendix 6

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BPSU ID:

Section 2: Diagnosis of Chylothorax

How was the diagnosis made? (Please tick)		Yes	No	Not Known
An accumulation of lymphatic fluid in the pleural space where:				
2.1.1	Clinician suspects a clinical diagnosis of a chylothorax, without pleural drainage.	☐	☐	☐
Above suspicion of chylothorax was due to:				
2.1.2	Pleural effusion on XR or Ultrasound – No drain inserted	☐	☐	☐
2.1.3	Timing of development of chylothorax	☐	☐	☐
2.1.4	Speed of accumulation	☐	☐	☐
2.1.5	Underlying clinical diagnosis	☐	☐	☐
2.1.6	Other:			
2.2	Pleural drainage is cloudy / opaque fluid is obtained, consistent with chylothorax, but no laboratory confirmation of the diagnosis has been sought.	☐	☐	☐
2.3	Triglyceride content >1.1 mmol/litre	☐	☐	☐
2.4	Total cell count > 1000 cells / microlitre	☐	☐	☐
2.5	Lymphocyte predominance >80%	☐	☐	☐
2.6	Other:			
2.7	Has the diagnosis of chylothorax been confirmed (Please tick)	☐ Yes	☐ No	
2.8	Date of diagnosis of this presentation (DD / MM / YY)	☐☐/☐☐/☐☐		

Section 3: Location of Chylothorax

3.1	Side of Chylothorax (please tick)	☐ Right	☐ Left	☐ Bilateral

1.

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BPSU ID:

Section 4: Mode of Presentation

4.1 Child's primary diagnosis: .....

4.2 Using the 'numeric code' below, please indicate in order of occurrence what was/were the actual, presumed or possible causes of the chylothorax:

Numeric Code:

Neonatal (congenital malformation) = 1	Neonatal (other) = 2	Cardiac (medical) = 3	Cardiac (surgical) = 4	Medical = 5
Oncology / Haematology = 6	Surgical (non cardiac) = 7	Trauma = 8	Not known = 9	Other = 10

4.2.1 Cause 1 ☐
4.2.2 Cause 2 ☐
4.2.3 Cause 3 ☐
4.2.4 Cause 4 ☐
4.2.5 Cause 5 ☐

Section 5: Interventional Procedures

Had the child undergone any procedural intervention prior to the chylothorax developing? (Please tick all that apply):

		Yes	No	Location (Please tick)
5.1	Thoracotomy	☐	☐	☐ Right ☐ Left ☐ Bilateral
5.2	Sternotomy	☐	☐	
5.3	Laparotomy	☐	☐	
5.4	Neck line insertion	☐	☐	☐ Right ☐ Left ☐ Bilateral
5.5	Chest drain insertion	☐	☐	☐ Right ☐ Left ☐ Bilateral
5.6	Surgical procedure e.g. oesophageal atresia repair, cardiac surgical repair	☐	☐	

5.7 Please clarify procedure: .....
5.8 Other interventional procedure .....

1.

Appendix 6

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BPSU ID:

Section 6: Management / Treatment

Please indicate all newly instigated management / treatment strategies:

	Management / Treatment (Please tick)	Date(s) started / undertaken	Date(s) stopped
6.1.1	☐ Pleural Catheter		
6.1.2	☐ Low Fat Diet		
6.1.3	☐ Medium Chain Triglycerides (MCT) diet		
6.1.4	☐ Total Parenteral Nutrition (TPN)		
6.1.5	☐ Octreotide / Somatostatin		
6.1.6	☐ Thoracentesis		
6.1.7	☐ Pleurodesis		
6.1.8	☐ Ligation of thoracic duct		
6.1.9	☐ Steroid therapy		
6.1.10	☐ IV Immunoglobulin (IVIG)		
6.1.11	☐ Other:		

Please indicate if the child had a pleural catheter (chest drain) for treatment of the chylothorax, and its location:

	Yes	No	Location (Please tick)		
6.2. Pleural catheter (chest drain(s))	☐	☐	☐ Right	☐ Left	☐ Bilateral
6.2.1 Already in situ	☐	☐	☐ Right	☐ Left	☐ Bilateral
6.2.2 Newly inserted	☐	☐	☐ Right	☐ Left	☐ Bilateral

Duration of chylous drainage from chest drain(s):

6.3 Right Chest Drain ---------- number of days

6.4 Left Chest Drain ---------- number of days

Management Strategy:

Was the Treatment / Management Strategy Chosen by:	Yes	No	Not Known
6.5 Physician preference	☐	☐	☐
6.6 Local Guideline or Protocol	☐	☐	☐
6.7 National Protocol	☐	☐	☐

6.8 Other .....

1.

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BPSU ID:

Section 7: Outcome from Diagnosed / Presumed Chylothorax

		Yes	No	Not Known
7.1	Resolution of Chylothorax	☐	☐	☐

If Resolution of Chylothorax:

7.2 Number of days to resolution from diagnosis ..... days

7.3 Number of days of treatment for the chylothorax ..... days

		Yes	No	Not Known
7.4	Is the child still receiving treatment?	☐	☐	☐

7.4.1 If 'Yes', what treatment? .....

Outcome:

		Yes	No	Died	Not Known
7.5	Has the child been discharged from hospital?	☐	☐	☐	☐

7.6 If discharged, what was their total length of stay in hospital during this admission? ..... days

7.7 If the child died (in hospital) please specify date of death (dd/mm/yy) ☐☐/☐☐/☐☐

7.8 What was the primary cause of death, as stated on the death certificate?
(please state if not known)

.....

Section 8:

Please use this space to enter any other information you feel may be important

Thank you, we are very grateful to you for completing this questionnaire

1.

Appendix 7 – 'RACHS-1' Categories

Risk Category	Individual Procedure by Risk Category
Risk Category 1	Atrial septal defect surgery (including atrial septal defect secundum, sinus venosus atrial septal defect, patent foramen ovale closure)
	Aortopexy
	Patent ductus arteriosus surgery at age ≥30 days
	Coarctation repair at age ≥30 days
	Partially anomalous pulmonary venous connection surgery
Risk Category 2	Aortic valvotomy or valvuloplasty at age ≥30 days
	Subaortic stenosis resection
	Pulmonary valvotomy or valvuloplasty
	Pulmonary valve replacement
	Right ventricular infundibulectomy
	Pulmonary outflow tract augmentation
	Repair of coronary artery fistula
	Atrial septal defect and ventricular septal defect repair
	Atrial septal defect primum repair
	Ventricular septal defect repair
	Ventricular septal defect closure and pulmonary valvotomy or infundibular resection
	Ventricular septal defect closure and pulmonary artery band removal
	Repair of unspecified septal defect
	Total repair of tetralogy of Fallot
	Repair of total anomalous pulmonary veins at age ≥30 days
	Glenn shunt
	Vascular ring surgery
	Repair of aorta-pulmonary window
	Coarctation repair at age ≤30 days
	Repair of pulmonary artery stenosis
	Transection of pulmonary artery
	Common atrium closure
	Left ventricular to right atrial shunt repair

Appendix 7

Risk Category	Individual Procedure by Risk Category
Risk Category 3	Aortic valve replacement
	Ross procedure
	Left ventricular outflow tract patch
	Ventriculomyotomy
	Aortoplasty
	Mitral valvotomy or valvuloplasty
	Mitral valve replacement
	Valvectomy of tricuspid valve
	Tricuspid valvotomy or valvuloplasty
	Tricuspid valve replacement
	Tricuspid valve repositioning for Ebstein anomaly at age ≥30 days
	Repair of anomalous coronary artery without intrapulmonary tunnel
	Repair of anomalous coronary artery with intrapulmonary tunnel (Takeuchi)
	Closure of semilunar valve, aortic or pulmonary
	Right ventricular to pulmonary artery conduit
	Left ventricular to pulmonary artery conduit
	Repair of double-outlet right ventricle with or without repair of right ventricular obstruction
	Fontan procedure
	Repair of transitional or complete atrioventricular canal with or without valve replacement
	Pulmonary artery banding
	Repair of Tetralogy of Fallot with pulmonary atresia
	Repair of cor triatriatum
	Systemic to pulmonary artery shunt
	Atrial switch operation
	Arterial switch operation
	Re-implantation of anomalous pulmonary artery
	Annuloplasty
	Repair of coarctation and ventricular septal defect closure
	Excision of intracardiac tumour
Risk Category 4	Aortic valvotomy or valvuloplasty at age ≤30 days
	Konno procedure

Risk Category	Individual Procedure by Risk Category
	Repair of complex anomaly (single ventricle) by ventricular septal defect enlargement
	Repair of total anomalous pulmonary veins at age ≤30 days
	Atrial septectomy
	Repair of transposition, ventricular septal defect, and subpulmonary stenosis (Rastelli)
	Atrial switch operation with ventricular septal defect closure
	Atrial switch operation with repair of subpulmonary stenosis
	Arterial switch operation with pulmonary artery band removal
	Arterial switch operation with ventricular septal defect closure
	Arterial switch operation with repair of subpulmonary stenosis
	Repair of truncus arteriosus
	Repair of hypoplastic or interrupted arch without ventricular septal defect closure
	Repair of hypoplastic or interrupted aortic arch with ventricular septal defect closure
	Transverse arch graft
	Unifocalization for tetralogy of Fallot and pulmonary atresia
	Double switch
Risk Category 5	Tricuspid valve repositioning for neonatal Ebstein anomaly at age ≤30 days
	Repair of truncus arteriosus and interrupted arch
Risk Category 6	Stage 1 repair of hypoplastic left heart syndrome (Norwood operation)
	Stage 1 repair of non-hypoplastic left heart syndrome conditions
	Damus-Kaye-Stansel procedure

Appendix 8 – Paper submitted for publication

A paper titled ‘Chylothorax in infants and children in the United Kingdom’ has been accepted for publication in the journal ‘Archives of Disease in Childhood’.

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