Nutritional status and its relationship with infection-related complications in children after cardiac surgery

by

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Abstract

There is little high-quality evidence investigating the relationship between preoperative nutritional status and clinical outcomes in children. Children with congenital heart disease are reported to be at increased nutritional risk. As healthcare associated infection, specifically surgical site infection (SSI), is a common postoperative complication, nutritional status prior to surgery may be one of few modifiable risk factors open to intervention in this patient group.

In this thesis, three interlinked studies explored links between nutritional status, with an emphasis on undernutrition, and postoperative infection-related complications in children after cardiac surgery. Firstly, existing evidence of this relationship following surgery in children < 18 years was systematically reviewed: 12 low-quality studies suggested a tentative association between undernutrition and postoperative infection-related complications, but lack of evidence on SSI.

A retrospective cohort study of 666 children undergoing cardiac surgery then explored whether undernutrition at time of surgery (weight-for-age z-scores (WAZ) less than two standard deviations below mean) was an independent risk factor for SSI. No relationship between undernutrition and SSI was found but neonatal age, preoperative Staphylococcus aureus carriage (OR 1.88, CI 1.01 – 3.07) and third or more cardiac reoperation (OR 5.41, CI 1.30 – 22.56) were independent risk factors. Furthermore, neonates who experienced the highest SSI rates, had low incidence of undernutrition. Consequently, a case study of 19 neonates explored postoperative feeding patterns and postoperative complications, including infection, during hospitalization following cardiac surgery. Four feeding patterns were identified. Those with more interrupted feeding patterns had more infections but less SSI and increased length of stay.

In conclusion, Staphylococcus aureus carriage should be targeted prior to surgery and during subsequent hospitalisation. There should be more research undertaken on the role of postoperative feeding in improving outcomes following neonatal cardiac surgery. Current methods of measuring SSI do not take into account competing risks from other infections potentially leading to erroneous conclusions about surgical performance.

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And finally, without having shared the experiences of the children and their families after cardiac surgery, this study would never have been conceived.

For my father.

Glossary of terms and abbreviations

Basic Aristotle Score (BAS) – consensus based, unadjusted risk score for paediatric cardiac surgery

CQUIN (Commissioning for Quality and Innovation) - a national payment framework that enables commissioners to reward excellence, by linking a proportion of the providers' income conditional to the achievement of ambitious quality improvement goals and innovations

Continuous venovenous haemofiltration (CVVH) - a temporary treatment for patients with acute renal failure used in an intensive care setting. Blood is passed through a tubing set via a machine to a semipermeable membrane where waste products and water are removed by convection. Replacement fluid is added before the blood is returned to the patient

ECMO – extra-corporeal membrane oxygenation

Extubation – the process of removing an endotracheal tube and the separation from invasive mechanical ventilation

Feeding disruption days – days on which the provision of enteral feeds was stopped for aspects of medical care or intervention

Feeding interruption pattern – a subjective classification system of the extent to which enteral feeding was affected during the postoperative hospital stay, including timing of feed initiation, feed disruptions, and ultimately the ability to achieve normal oral feeding

Feeding intolerance – inability to tolerate the administration of enteral feeds, leading to a reduction in nutritional requirements

FiO_2 – inspired fraction of oxygen

Gastrostomy tube (GT) – a feeding tube passed through the abdominal wall into the stomach, for the administration of enteral feeds and medications

HAI – Healthcare-associated infection

Inotrope – a medication used to maintain blood pressure in situations of low cardiac output

ICU – intensive care unit

Lactate – Serum lactate is the most commonly used point-of-care biomarker in intensive care settings, used as an indirect measure of the adequacy of tissue oxygenation for the identification of high-risk patients and to monitor response to therapeutic interventions

Nasogastric tube (NGT) – a feeding tube passed via the nares into the stomach for the administration of enteral feed and medications

Necrotizing enterocolitis (NEC) – pathology compromising the intestinal mucosal barrier with invasion of pathogenic bacteria and resultant injury to the intestinal wall. The process can lead to bowel ischaemia, bowel perforation, sepsis and death

Onodera's Prognostic Nutritional Index (PNI) – a nutritional screening tool based on serum albumin levels and white cell count

PaO_2 – partial pressure of oxygen

PRAiS – Partial risk adjustment in surgery. Used by NICOR (National Institute for Cardiovascular Outcomes Research) for surgical risk profiling and outcomes across paediatric congenital heart centres

PIM2 - Pediatric index of mortality, a severity scoring system used for predicting outcome of patients admitted to intensive care units

Reintubation – the reinsertion of an endotracheal tube after a failed attempt at extubation

SSI – surgical site infection

Vasoactive inotrope score (VIS) – a score to quantify the amount of cardiovascular support received after congenital heart surgery and used as a predictor for postoperative morbidity and mortality

Ventilator – a machine used to maintain or support breathing when there is an endotracheal tube in place

Chapter One: Introduction to the thesis

1.1 Introduction

This chapter commences with the rationale for the thesis and the relationship of this work to the context of my clinical practice is explained. In addition, a reflection on the complexities inherent within the dual role of clinician-researcher will be discussed along with the impact this has had on the design and conduct of the study. Following this, a background section introduces the key topics around which the thesis revolves. Finally, the overall structure of the thesis is explained to orientate the reader to the format used in presenting the thesis findings.

The rationale for choosing to research this subject area was primarily driven by my role as a Consultant Nurse working in Paediatric Cardiac Surgery (PCS). It became apparent after introducing a formal monthly PCS mortality and morbidity meeting in 2008 that the department was seeing a consistently high rate of surgical site infection (SSI); SSI was the most frequently reported postoperative complication. Despite the subsequent implementation of a best practice-based care bundle, which will be discussed in further detail in later chapters, the rate of SSI did not reduce. As a large proportion of clinical time was subsequently spent managing these wound infections, both in hospital and post discharge, I became interested in gaining further insight and understanding into those modifiable demographic, procedural and/or treatment factors, associated with an increased risk of SSI. This could help identify potential preventative measures for paediatric cardiac care services to enhance the quality of care for patients, reduce surgical morbidity and improve service efficiency through reducing length of hospital stay. As all clinicians have a clinical and moral responsibility to review and revise treatment based on observed outcomes, this research evolved through an aspiration to improve the longer term outcomes for children after PCS which extend beyond initial hopsitalisation.

Clinical experiences and my knowledge of professional practice has been a great influence in the design and conduct of the research described in this thesis. My clinical involvement in the cardiac surgical patient pathway, from preoperative clinic through surgery, intensive care, cardiology ward and outpatient clinic, provided me with additional insight which was advantageous and influential in shaping and refining the stages of this research project. Acknowledging prior clinical experience has been recognized by McNair et al (2008) as being characteristic of clinician-researchers. My involvement had both advantages and disadvantages; it was advantageous because I was familiar with the clinical environments in which care delivery took place and could easily transfer my clinical skills and attributes into a

research perspective. Possessing knowledge of the practice and terminology used in these areas can facilitate the generation and dissemination of clinically relevant research (Chew-Graham et al, 2002). However, the potential for role conflict between my professional practice and research practice was a disadvantage, in that there were differing and sometimes competing goals between them - having a clinical goal focused in the present and aspiring to maximize the benefit for my existing patients, versus a research goal which was to observe, consider and generate new knowledge for the potential benefit of my future patients (Hiller & Vears, 2015). As a result, I had concerns that I would be unable to adopt a wholly non-clinical research identity, especially as it was a consequence of my clinical expertise which was responsible for wanting to initiate a study into a clinically based problem. I was aware that this distinction may also present difficulties for the clinical staff who were well-used to my clinical presence and active decision-making, therefore in a research role I did not want to influence or direct care, moving interchangeably from one role to the other may have been a potential source of confusion. Also, I would be transitioning from a position of clinical expertise to novice researcher, and this was a prospect of simultaneous excitement and trepidation. In order to address these concerns, an early decision was made to clearly separate my clinical time from research time.

Choosing to research an aspect related to surgical outcome at a time when paediatric heart surgery in England was under national review (DoH, 2010; NHS England, 2017) may be considered foolhardy. Added to which the stimulus to investigate SSI was due to high complication rates, therefore I was aware at the outset that my research journey might not always be a comfortable one. Having to consider these salient factors brought to the study a heightened appreciation of the importance of the research question, fundamentally reinforcing my sense of professional responsibility in attempting to address and influence a positive change for the ultimate benefit of patients.

1.2 Background

To provide some context to the issues that will be discussed within this thesis this section provides a brief overview of the relevant subject matter, which will be explored further in later chapters. In addition, as paediatric cardiac surgery (PCS) is a highly medicalised and complex intervention spanning multiple healthcare disciplines and clinical areas, this will form the foundation for the more detailed explanations and discussions which will be incorporated into the individual study chapters.

1.2.1 Healthcare-associated infection

For the purpose of this research, infection-related complications are defined as those complications which occur after surgery as a result of infection. As such, therefore, they are specific examples of healthcare-acquired infection.

Healthcare-associated infection (HAI) is defined by Public Health England (PHE, 2016) as infections when the onset of symptoms occurs on or after day 3 of hospital admission or when readmission occurs less than 48 hours after day of discharge from an acute care hospital or within 30 days of a surgical procedure (90 days if an implant[1] is placed during surgery (PHE, 2013, p. 15). In 2011, a national point prevalence healthcare-associated infection survey undertaken in all patients admitted to acute-care hospitals indicated a prevalence rate of 6.4% (PHE, 2016). Consequently, HAI poses a considerable burden to healthcare systems worldwide (Ridelberg & Nilsen, 2015) and remains as a significant cause of morbidity and mortality (Turcote et al, 2014; Barker et al, 2010; Grisaru-Soen et al, 2010).

HAI have been observed in 5 – 10% of all hospital admissions in the USA and Western Europe (Humphreys et al, 2008). Both U.S. and European governmental organisations have developed strategies and policies to reduce the HAI incidence and reduce the added cost to healthcare, however, despite substantial preventative effects there is still room for improvement (Godamunne et al, 2016). Epidemiologic evidence in adults demonstrates the connection between malnutrition and HAI - an analysis which included 887,189 adult patients from 138 hospitals found that malnourished patients are twice as likely to have surgical site infection, and five times more likely to have mediastinitis following coronary artery bypass grafting (Fry et al, 2010). Demling et al (2009) demonstrated a 10% loss in lean body mass results in immune suppression and increases infection risk, whereas losses greater than 15% is associated with impaired wound healing. The link between malnutrition and infection in adults, therefore, has been long established, with recommendations that the identification and treatment of malnutrition should be considered a component of HAI reduction strategies. In adults, therefore, it is recognized that the success of surgery depends on both technical surgical skills and the ability of the patient to carry the additional metabolic load incurred, which in turn is dependent on the provision of appropriate nutritional support (Weimann et al, 2017).

Public Health England, formerly the National Nosocomial Infection Surveillance (NNIS), has undertaken mandatory surveillance of key HAI in England since 2001. Case level methicillin-

[1] Implants are defined as a non-human foreign body that is placed permanently in the patient during an operation and is not routinely manipulated for diagnostic or therapeutic purposes (PHE, 2013).

resistant Staphylococcus aureus (MRSA) reporting was introduced in 2005, with Clostridium difficile infection (CDI) in patients over 2-years old introduced in 2007. Mandatory surveillance for methicillin-sensitive Staphylococcus aureus (MSSA) and Escherichia coli was introduced in 2011. In addition to this national mandatory surveillance requirement, the study hospital where this research was undertaken were voluntarily reporting central-line associated bloodstream infection (CLaBSI) and ventilator-associated pneumonia (VAP), along with surgical site infection (SSI) following PCS and neurosurgical procedures and reported formally at the quarterly Infection Prevention and Control Committee meeting, chaired by the Director of Infection Prevention Control for the hospital.

Consequently, despite the advances in survival, postoperative infection-related complications remain a significant cause of morbidity and in-hospital mortality in 6 – 30% of children undergoing PCS (Hatachi et al, 2018), leading to increased hospital length of stay and medical expense (Umscheid et al, 2011). The existing evidence regarding the link between undernutrition and postoperative infection-related complications is less well defined than in the adult surgical population.

1.2.2 Undernutrition in children

Undernutrition - as one form of malnutrition - can be defined as an imbalance between nutrient requirement and intake, resulting in cumulative deficits of energy, protein or micronutrients that may negatively affect growth, development, and other relevant outcomes (Mehta et al, 2013). Due to the high nutrient requirements for growth and the body composition of the young infant they are especially vulnerable to undernutrition (Thilo & Rosenberg, 2005). Limited fat stores of the very young infant mean that energy reserves are unusually restricted, and the relatively large size and continued growth of the brain render the central nervous system especially vulnerable to the effects of malnutrition in early postnatal life (Krebs et al, 2005).

There is an accumulation of evidence that nutrition and growth in early life can have substantial influences on adult health (Robinson & Fall, 2012), although it must be acknowledged that most of the literature describing outcomes following early faltering growth is from 20 - 30 years ago (Lardon-Noth et al, 2018). Important developments of the brain and cognitive processes take place during the first three years of life (McCall et al, 1972) and there is evidence that exposure to early undernutrition is associated with later deficits in neuro-behavioural development, cognition, motor performance and behaviour (Grantham-McGregor et al, 2000). Black et al (2007) found increased vulnerability to short stature, poor arithmetic

performance and poor work habits at 8 years of age in those children who experienced failure to thrive during infancy compared to similar children with adequate growth. Similarly, Dykmon et al (2001) studied 27 school children aged 8 – 12-years with earlier failure to thrive during infancy to a normal, socioeconomically matched control group and reported statistically significant differences in height, weight, IQ and clinically adverse attention and aggression ratings compared to the controls. In addition, 60% had remained below the 20th percentile for weight, with 48% below the 20th percentile for height. More recent studies into the consequences of early growth failure are lacking (Larson-Nath & Goday, 2016).

High nutritional requirements and limited fat stores place healthy infants and young children at potential risk of undernutrition - and in view of the long-term sequelae early faltering growth may have on long term outcomes, is a primary reason why growth monitoring is performed in early childhood years (Rudolf & Logan, 2005). For those children who require hospital admission during their early childhood years an additional burden is placed, with recent evidence suggesting all children admitted to hospital experience a deterioration in their nutritional status (Pichler et al, 2014), which is compounded in the presence of chronic or critical illness (Pawellek et al, 2008; Delgado et al, 2008). Consequently, any child with congenital heart disease will, in addition to condition-related undernutrition, be at additional risk as they will require repeated hospitalization for diagnostic and therapeutic interventions including surgery.

1.2.2.1 Approaches to nutritional assessment in children

A standardized approach to the recognition and diagnosis of undernutrition in the paediatric population is lacking, and controversy surrounds what is the best and most useful approach (Becker et al, 2014). Consequently, the routine assessment of nutritional status, particularly in high-risk children, is often sporadic and inconsistent and requires a combination of different assessment approaches (Maqbool et al, 2008).

The cornerstone of an optimal nutritional approach is to evaluate the nutritional status of the child, detect undernutrition, define nutritional goals, and adapt nutritional intakes accordingly (Valla et al, 2018). As growth is the primary outcome measure of adequate nutritional status in children (Mehta et al, 2013; Carney et al, 2010; WHO, 1995), growth charts have been designed so that growth trends in the individual child can be observed over time (CDC, 2014). Growth charts which facilitate comparison of units of standard deviation from norms for reference age groups – *z*-score comparison - have been recommended for tracking and assessing nutritional status in children (Mehta et al, 2013; WHO, 2014). These comparisons include length-for-age, weight-for-age, head circumference-for-age, and weight-for-length. For

children over 2 years, body mass index (BMI)-for-age can also be used (Becker et al, 2014). However, growth charts are not intended for use as a sole diagnostic instrument but should contribute to the formation of an overall clinical impression of the child being assessed. For most children, however, these relative growth measurements along with dietary history and physical examination, will sufficiently assess nutritional status and growth (Kleinman & Greer, 2013).

Children with identified nutritional compromise warrant a more comprehensive nutritional assessment, with management by a multidisciplinary team. A full dietary history, including exploration of dietary intake, appetite and satiety (Wisken et al, 2015) has been recognized as an important component. Ideally this should incorporate the physical and emotional response to food, in addition to an estimation of intake relative to dietary reference values . In addition to intake, assessment of output may also be useful - high stool losses may represent malabsorption of nutrients or secretory/osmotic diarrhoea, both of which may have significant nutritional consequences, similarly profuse vomiting will make it difficult for children to achieve a normal dietary intake. Outside of infancy (when it is relatively easy to assess macronutrient intake from enteral feed volumes and output from nappies), the quantitative evaluation of dietary intake may be more challenging and 3- to 5-day food diaries may be required in order to identify nutrient inadequacies or to evaluate relationships between diet and biological parameters of chronic disease (Kleinman & Greer, 2013). Drug-nutrient interactions may occur and alterations in drug metabolism and absorption caused by food or pharmacologic interactions may be clinically significant (Maka & Murphy, 2000).

Laboratory based assessments may be an adjunct to detailed investigation when faltering growth has been identified, particularly in situations where clinical examination points towards single nutrient deficiency or underlying systemic disease. Currently there are no serum biomarkers which are not influenced by non-nutritional variables, such as acute metabolic stress and inflammation, demonstrate convincing evidence of a relationship with clinical outcomes in children (Ong et al, 2014). In addition, there are no established ranges for prealbumin and retinol-binding proteins in young children (Wessner & Burjonrappa, 2014) therefore they are not routinely undertaken in paediatric practice (Wisken et al, 2015).

More advanced anthropometric techniques, such as mid-upper arm circumference (MUAC), triceps skinfold thickness (TSFT) and bioelectrical impedance studies, may be useful. These tests assess body composition and aim to calculate fat mass from fat free mass. However, as these techniques require both specialist training and equipment applicability and reliability outside of a specialist multidisciplinary team is limited.

For children admitted to hospital, current UK guidance states that assessment of hydration and nutrition should be part of the assessment process (Brotherton et al, 2010), in addition to basic anthropometry. It has been recognized that some children with faltering growth on hospital admission will be missed by simple anthropometric measures (Wisken et al, 2015), therefore nutritional screening assessments have been introduced. Although a variety of paediatric screening tools have been developed and validated for use (Joosten & Hulst, 2014) the only common variable between them is some estimate of dietary intake. However, despite the existence of these tools they have not been routinely implemented into paediatric practice. Evidence suggests that even basic measuring and plotting of weight and height does not routinely happen (Grek & Puntis, 2013) so improvement is required in ensuring the basics are done correctly. Despite recognition that children with acute and chronic illness are at most nutritional risk (Grover et al, 2009), poor nutritional assessment practices will mean undernutrition will continue to remain undetected and unaddressed (Larsen et al, 2014; Pichler et al, 2014).

1.2.3 Congenital heart disease

Approximately one in every 1,000 babies is born with a heart or circulatory condition (Franklin et al, 2017). Most children with congenital heart disease requiring surgical intervention will present within the first year of life (Gazit et al, 2010), and although most of the major heart malformations are detectable during foetal life (Allan et al, 2000), antenatal diagnosis remains skewed towards the severe end of the anomaly spectrum (Dhillon et al, 2006). Current data shows in a quarter of babies born with congenital heart disease the defect will be detected by antenatal ultrasound scans, and for those babies with more complex lesions the rate increases to at least 80%, as such severe defects are more easily seen by an obstetric sonographer (Marek et al, 2011). However, in England two in three babies with major congenital heart disease remain undiagnosed antenatally and the current newborn examination will fail to detect one in three with life-threatening major congenital heart disease before they leave hospital (Gardiner et al, 2014). Failure to recognize and promptly treat major congenital heart disease is associated with increased morbidity and mortality rates (Boyd et al, 2005; Brown et al, 2006) and this has been recognized as an important quality-of-care issue (Gardiner et al, 2014).

There are some defects, however, that cannot be predicted from foetal life including a patent ductus arteriosus and secundum type of atrial septal defect, since these are components of foetal circulation (Figure 1.1). In addition, some types of ventricular septal defect may also be difficult to detect, because of their size or position (Dhillon et al, 2006). For those children

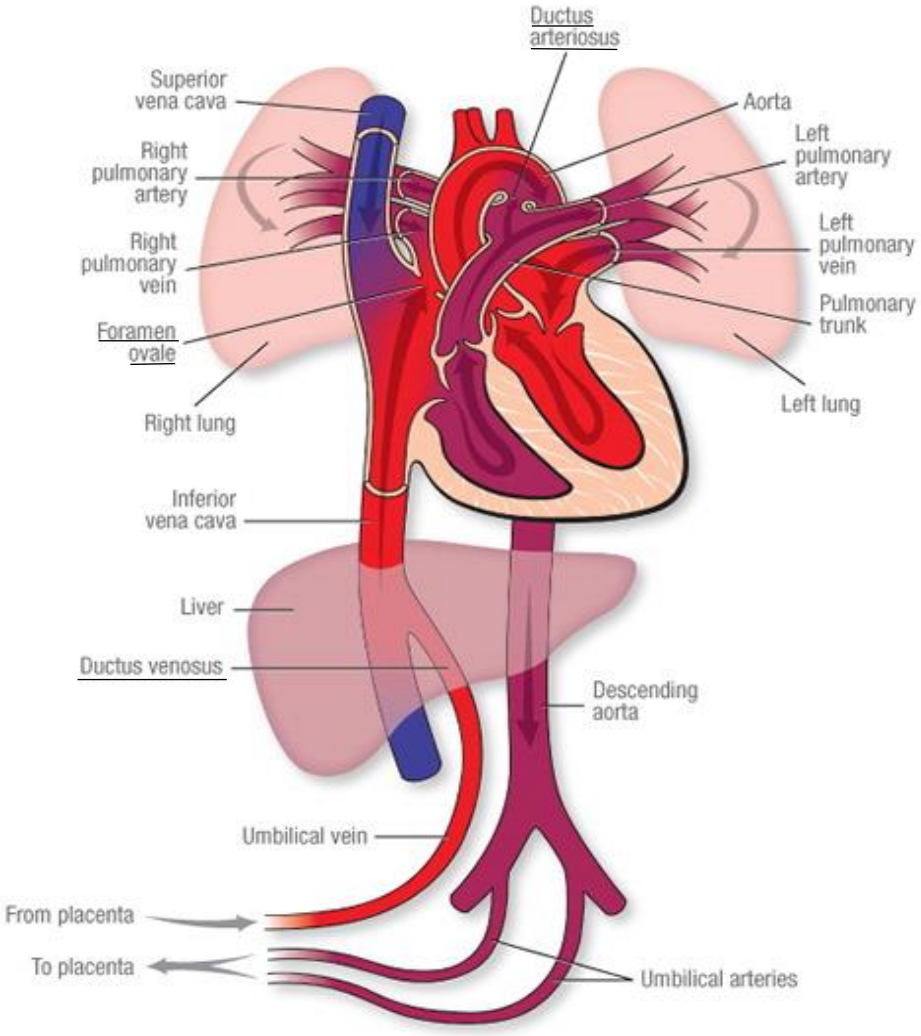
without the advantage of being antenatally diagnosed, presentation will depend on the nature of their underlying pathophysiology.

Malformations of either the pulmonary (lung) or systemic (body) circulation are usually duct-dependent lesions, and, if undiagnosed at birth will usually present in haemodynamic collapse during the first two to three weeks when the ductus arteriosus closes (Momma, 2012), often with a suspected diagnosis of neonatal infection. In the full-term newborn, breathing creates a rise in circulating oxygen that causes this ductal closure by inhibiting the synthesis of prostaglandins from the ductal tissue (Noble et al, 2010). As the ductus is a structure which connects the pulmonary and systemic circulations, it compensates to some degree for malformations in either the left or right ventricular outflow tracts, which cause obstruction to the circulation. Antenatal diagnosis in this group of neonates can be life-saving as, once the baby is born, synthetic prostaglandin can be administered intravenously to maintain ductal patency until surgery can be scheduled, ensuring oxygenation can be maintained and preventing the hypoxaemia and cyanosis, which are common presentations of severe congenital heart disease.

Cyanosis is a physical resulting from the presence of deoxygenated haemoglobin in the blood at a concentration of at least 5g per decilitre. It is characterized by a slate-blue colour of the mucous membranes, nail beds, and skin and is a feature of congenital heart disease caused when there is reduced oxygenation of blood in the central arterial tree. This will be due to the mixing of partially desaturated (venous) blood and normally saturated (arterial) blood (Noble et al, 2010). Cyanosis will occur whenever desaturated blood can directly enter the systemic circulation, for example, Tetralogy of Fallot, where venous blood entering the right ventricle, unable to easily exit the heart via the right ventricular outflow tract due to pulmonary stenosis, will pass through the ventricular septal defect to the left ventricle before leaving the heart via the aorta.

Figure 1.1 Normal foetal circulation

The three components of the foetal circulation are shown underlined: i) foramen ovale, ii) ductus arteriosus, iii) ductus venosus.



Source: From the public domain via www.doctorsgates.blogspot.com 10 May 2018

This is an example of a cyanotic congenital heart malformation where there is inadequate pulmonary (lung) blood flow and oxygenation, the severity of which will be determined by the extent of the obstruction to blood leaving the right ventricle through the pulmonary valve, and the existence of a patent ductus arteriosus (which as has already been previously identified, will provide a route of blood flow to the lungs). This condition, therefore, results in varying degrees of hypoxaemia which is a state of abnormally decreased arterial blood oxygen concentration. Although often related, the degree of hypoxaemia may or may not depend on the physical sign of cyanosis, depending on blood haemoglobin concentration (Driscoll, 2006).

For those children not presenting with an acute life-threatening event in the early neonatal period, presentation is usually within the first three to six months of life from signs and symptoms of congestive heart failure and/or growth failure (Driscoll, 2006). In this group, anti-failure medication is commenced, and elective cardiac surgery can be scheduled according to symptoms. Any presentation beyond the first year of life is usually due to an incidental finding during routine examination; namely, a heart murmur associated with or without poor growth and, occasionally, systemic hypertension due to coarctation of the aorta, which is a narrowing of a discrete portion of the descending aorta usually below the level of the ductus arteriosus. These children will usually be asymptomatic but will require surgical inteervention nonetheless.

1.2.4 Undernutrition and congenital heart disease

Faltering growth – previously termed failure to thrive (NICE, 2017) - is a common presentation in infants with congenital heart disease. This symptom will usually be due to a combination of poor feeding caused by breathlessness, coupled with the increased energy requirements due to the compensatory increases in heart rate required to maintain adequate circulation (Nydegger et al, 2009). With the relative reduction in systemic blood supply caused by heart failure, heart rate increases to maintain cardiac output. Cardiac output can be manipulated by one or all of three mechanisms; increasing muscle fibre stretch (compliance), increasing venous return to the heart (preload) or increasing heart rate (stroke work). However, as babies and young children have relatively fixed compliance of cardiac muscle fibres their ability to raise cardiac output is mainly dependent on increases in heart rate (Lerman et al, 2016).

Congenital heart disease will generally cause pressure or volume overloading of the heart. Pressure overloading, such as in aortic stenosis, results from an obstruction to the left ventricular outflow tract with reduction in forward flow of blood into the aorta and a subsequent reduction in stroke volume. Volume overloading is commonly seen with isolated

ventricular septal defects (VSD), resulting from the pulmonary recirculation which occurs with the left to right shunting of blood at ventricular level. This increases the volume of blood returning to the left side of the heart from the lungs and in this situation, standard medical management of this high output cardiac failure is diuretic use (Noble et al, 2010), which has been associated with the loss of certain micronutrients in urine (von Haehling et al, 2009; Witte et al, 2001) and, possibly has an additional deleterious effect on nutritional status.

1.2.5 Surgery for congenital heart disease

Historically, before the advent of and widespread availability of cardiopulmonary bypass, all attempts to surgically intervene in children with congenital heart disease were palliative in nature (Scheurer & Atz, 2009). The first surgical palliation for an adult with Tetralogy of Fallot was a subclavian artery to pulmonary artery shunt (BT shunt) performed in 1944 by Blalock & Thomas (Blalock & Taussig, 1945). This shunt functions physiologically like the patent ductus arteriosus, with lung blood supply coming from a smaller, less pressurised subsidiary branch of the aorta rather than the aorta itself. In 2007, Williams et al reviewed the John Hopkins Hospital's BT shunt experience in the intervening 62 years since this first landmark case reporting a 14% overall mortality rate, with 41% of patients subsequently undergoing total repair of Fallot's tetralogy.

On 6th May 1953, the Gibbon-IBM heart-lung machine was used successfully by Dr John Gibbon during the intra-cardiac closure of an atrial septal defect in an 18-year-old female, although immediate subsequent attempts in subsequent patients were less successful (Gibbon, 1954). In the following 60 years, contemporaneous techniques and procedures have reflected the rapidly advancing technological achievements of both the designers and operators of cardiopulmonary bypass systems; it is now routine to surgically correct or palliate congenital heart disease in patients weighing as little as 2.5kg, with dramatic improvements in survival rates across all procedures (Ades et al, 2010; Kalfa et al, 2014; Kalfa et al, 2015)

However, both corrective and palliative surgery for congenital heart disease is not without risk. Trying to accurately predict this risk has led to the development of a plethora of risk-adjusted scoring systems for congenital heart disease (Lacour-Gayet et al, 2004; Jenkins et al, 2002; Pagel et al, 2013). Patient age, weight, complexity, hospital volume and surgeon volume are five significant variables reported to affect risk and outcome (Gazit et al, 2010). Predicting risk and adjusting for patient-related factors provides a way to not only predicting mortality, but in the process of doing so, also provides a benchmark against which actual mortality can be assessed which also provides a mechanism for quality control (Nashef, 2015).

Along with these technological advances which make surgery safer, increased scrutiny and transparency regarding survival rates have led to a significant reduction in 30-day mortality. Franklin et al (2017) report a 30-day mortality of 2.1% for the 3-year period between 2013 and 2016 for procedures among children 0 to 16 years. This ranged between 0.8% and 3.5% among the 13 congenital cardiac centres in the UK. The authors suggest that given this low 30-day mortality, there must now be "a commitment to move beyond 30-day survival rates and explore methods to assess longer term survival, the incidence of post-procedural complications, and other measures of functional outcome in survivors" following palliation or correction of congenital heart disease (Franklin et al, 2017, p. 9). Indeed, continuing to focus solely on 30-day mortality will overlook 96% of children who survive to hospital discharge and the important morbidity that they may experience (Jacobs et al, 2011).

1.3 Statement of the problem

Adequate nutrition is vital for the physical and cognitive development of all children. The risk of undernutrition increases with the presence of a chronic diagnosis such as congenital heart disease and with hospital admission. Although the evidence that preoperative undernutrition in adult surgical populations is associated with increased morbidity and mortality has been well reported in the literature (Weimann et al, 2017), similar evidence in children is lacking. This research will explore the relationship between undernutrition and postoperative infection-related complications in children undergoing surgery for congenital heart disease, to determine whether nutritional status influences postoperative outcome.

1.3.1 Purpose of the programme of studies

The main purpose of the research was to explore undernutrition as a potentially modifiable factor influencing infection complications, in particular surgical site infection, in children following paediatric cardiac surgery.

1.3.2 Objectives of the programme of studies

The principle objectives, therefore, were to:

1. determine the existing level of evidence between undernutrition and infection complications in children after surgery
2. investigate preoperative factors, including undernutrition, as risk factors for a specific type of infection (surgical site) in a specific population (following cardiac surgery)
3. explore the role of postoperative feeding patterns with outcomes, including infection, in a high risk paediatric cardiac surgical population.

1.4 Structure of the thesis

In the following section of this chapter an overview of the plan of the thesis structure and methods of investigation will be presented to introduce the way the thesis has been organised. The research was undertaken in three independent but linked studies using both analytical and case study research methods which is in keeping with the epidemiological methodology used when studying associations between disease and its possible causes.

Chapter One, this chapter, provides an introduction to the work contained in the programme of studies.

Chapters Two to Four report the three individual stages of the research project: stage 1, the systematic review; stage 2, the retrospective cohort study; and stage 3, the case study. Each of these chapters begins with a background section to provide context to the study objectives and discussion of the relevant literature and perspectives which frame the existing knowledge base. The aims and objectives of the individual study, the rationale for the study design, the methods used, and the data collection and handling procedures will be presented and discussed, along with any ethical considerations, prior to presenting the results and analysis of the study. Study credibility will be considered within the appropriate framework given the chosen methodology. Each chapter will conclude with a discussion and summary of the study findings and the conclusions and recommendations that can be drawn. Where relevant, the findings from stage one and two are used to inform the design and conduct of the following study. An overview of the research design and methods for the three research chapters are presented below.

Chapter Two reports the first stage of the research, a systematic review to assess the evidence to date for a relationship between undernutrition and infection-related complications after surgery in children. It begins with a brief summation of the background literature addressing current evidence, prior to presenting the work undertaken. Findings were suggestive of a tentative relationship between undernutrition and infection-related complications, apart from SSI, but the overall quality of included studies was low. However, for those studies undertaken in paediatric cardiac surgical populations, the direction of effect appeared to support this relationship, warranting further investigation.

Chapter Three, therefore, follows on from the findings in Study One and reports the second stage of the research, which is a retrospective cohort study determining the incidence of surgical site infection in children after paediatric heart surgery, and to investigate if nutritional

status – undernutrition in particular - is an independent risk factor for surgical site infection. A background section provides additional definitional and contextual information, which facilitates understanding methodological anomalies apparent in the results and discussion of the study findings and reflects the complexity of outcome measures in the highly complex system which is paediatric cardiac surgery. Findings identified neonates as being at the highest risk of SSI, but unexpectedly identified that being of low weight-for-age at time of surgery appeared to be protective against SSI. These unanticipated neonatal findings warranted further exploration, as the greatest SSI risk reduction would occur for this age group.

Chapter Four, consequently, reports on the final stage of the research, which is a case study exploring postoperative neonatal feeding up to the point of hospital discharge (or 6-weeks for those of remaining inpatients) following PCS, arising directly from findings in the previous two stages of research. In Study 1, neonates were found to be underrepresented in the surgical populations included in the review, with Stage 2 identifying this age group as being most at risk of SSI despite a low incidence of undernutrition at the time of surgery. Also, following model performance there was the realisation that important factors influencing surgical site infection risk in the neonatal population may be postoperative rather than preoperative. Relationships between enteral feeding and postoperative outcome were explored and the postoperative feeding patterns identified were suggestive of a link with surgical outcomes.

Chapter 5 is the discussion chapter; it begins with a brief synopsis of the individual study findings prior to integrating and synthesising the unifying themes identified across all studies and placing them in the context of existing knowledge before proposing a new understanding of infection-related complications after paediatric cardiac surgery. The original contributions to knowledge are discussed and a summary of the strengths and limitations of the research is presented. By proposing a new theory regarding SSI development, the implications for practice and future research are addressed including challenging the existing approach to measuring absolute complications, rather than the outcome of those complications, as an indicator of quality care.

Chapter Two: A systematic review to determine if undernutrition is a risk factor for postoperative infection complications in children

2.1 Introduction

This chapter begins with a summary statement of undernutrition which will be used as the basis of understanding for the thesis. A brief synopsis for the origin of the relationship between undernutrition and surgical outcomes is provided, prior to the background of the systematic review which assesses the current level of existing evidence in children after surgery. A systematic review methodology was chosen as some evidence was known to exist in this area, but no review investigating the relationship between undernutrition and infection-related complications had been undertaken. Additionally, undertaking a systematic review would allow an objective appraisal of the existing evidence and its quality, by two independent reviewers, which is an advantage over a more traditional narrative review (Egger et al, 2001). Consequently, the chapter follows the methods advocated by the Cochrane Collaboration (Green & Higgins, 2011) in undertaking systematic reviews as far as they apply to observational studies. Finally, a closing summary positions the review findings within the context of the programme of studies, and the direction of ongoing study.

2.2 Background

Nutritional status is an important determinant of growth and health (Hendrikse et al, 1997). There is evidence that nutritional status deteriorates in both adults and children following hospital admission (Sermet-Gaudelus et al, 2000; Aurangzeb et al, 2012; Pichler et al, 2014), often when associated with chronic or critical illness (Pawellek et al, 2008; Delgado et al; 2008). An association between undernutrition and poor surgical outcome was first reported by Studley in 1936. Seventy years later, variations of this association continue to be of clinical interest and are studied within both the adult and paediatric populations (Almeida et al, 2013; Cabrera et al, 2012; Cerantola et al, 2013; Eskedal et al, 2008; Karateke et al, 2013).

Adult studies have demonstrated after adjusting for other risk factors, such as age and severity of illness, pre-operative nutritional status has been a reliable indicator of the incidence of post-operative complications (Lavernia et al, 1999). In undernourished preoperative adult patients, the incidence of postoperative adverse events (delayed wound healing, bacterial infections, extended length of stay) is reported to be higher than in those patients with normal nutritional status (Bozzetti, 2002). Schneider et al (2004) studied the incidence of hospital acquired

infection in a university hospital in Nice, France, and found malnutrition to be independently associated with a higher prevalence of infection.

In children, the relationship between surgical outcomes and nutritional status has not been so thoroughly investigated. However, there is evidence to suggest that nutritional status deteriorates in children following hospital admission (Aurangzeb et al, 2012; Pichler et al, 2014), and is most often associated with chronic or critical illness (Delgado et al, 2008; Pawellek et al, 2008). Poor nutritional status (as measured by low weight-for-age z-scores) has been associated with increased duration of mechanical ventilatory support, increased length of intensive care stay, and increased one-year mortality in neonates after cardiac surgery (Mitting et al, 2015), with other supporting evidence that inadequate enteral protein intake and extremes of weight percentile are associated with increased mortality in critically ill children (Larsen et al, 2013; Mehta et al, 2015, Numa et al, 2011). As children after surgery are likely to be critically ill, and may even require intensive care postoperatively, the potential relationship between undernutrition and infection-related outcomes is a pertinent one.

A recent evidence-based review of the literature found weak evidence supporting poor preoperative nutritional status predicting adverse outcomes in paediatric surgical patients (Wessner & Burjonrappa, 2014). However, this review identified only six studies which explored preoperative nutritional status with adverse post-operative complications, of which only two studies reported infection-related complications as their primary outcome.

Although nutrition is recognized as being essential for any child in order to achieve growth with normal mental and psychomotor development (Corbett & Drewett, 2004; Lucas et al, 1998; Rudolf & Logan, 2005), and following surgery will be particularly essential for healing and return of organ tissue function, little evidence exists linking poor nutritional status with adverse postoperative outcome. Additionally, although Briassoulis et al (2001) measured the frequency of acute and chronic malnutrition within paediatric intensive care in order to investigate the influence of an early enteral feeding regime, this study reported an increase in nutrition indices and acute phase protein levels, but the benefit in terms of improved clinical outcome was less clear.

In summary, there is evidence suggesting a relationship between undernutrition and adverse postoperative outcome in adults. To date, the exact relationship between nutritional status and adverse infection-related complications has not been evaluated in a systematic way within the paediatric surgical population. This review will provide relevant information both on how children are being nutritionally assessed prior to surgery, and how undernutrition may impact on postoperative healthcare acquired infection and its longer-term morbidity.

2.3 Aim of the study

To determine the existing level of evidence between undernutrition and infection complications in children after surgery

2.3.1 Description of the exposure (undernutrition)

Undernutrition as categorized by any method of nutritional assessment (anthropometric, biochemical or applied screening tool) routinely or experimentally measured in a paediatric surgical population.

2.3.2 How the exposure might work

Undernutrition identified pre-operatively will be explored as a potential risk factor for infection-related complications after surgery in children, as nutritional depletion can lead to compromised wound healing and decreased immune function (Rogers et al, 2003), predisposing children to infection.

2.3.3 Description of the outcome (infection)

Postoperative infection complications robustly defined within the study methodology, and with a clearly stated duration of follow up.

2.3.4 Why it was important to do this review

If a relationship between undernutrition and adverse infection-related outcomes in a paediatric surgical population was suggested through a systematic review of the literature, further research would be warranted into both the benefit of using nutritional assessment methodology as part of risk stratification processes, and the consideration of nutritional interventions either pre-, intra- or postoperatively in order to optimize nutrition and improve surgical outcome.

2.4 Methods

2.4.1 Criteria for considering studies in this review

A summary can be viewed in Table 2.1.

2.4.1.1 Types of studies

Any quantitative study design reporting infection-related complications in children (<18 years) and evaluating preoperative nutritional status. These include:

- Prospective inception cohort studies;
- Retrospective cohort studies;

- Case control studies where cases were children with post-operative infection-related complications;
- Controlled trials when the control group did not undergo active nutritional intervention as part of standard care.

Studies utilizing cross-sectional methodology, case series or case study design were not included.

2.4.1.2 Types of participants

Children less than 18 years of age, requiring surgical intervention for treatment or management of an acute or chronic condition, within a hospital setting.

Table 2.1 : Criteria and search terms for the identification of eligible studies

Methodology	**Participants**	**Exposures**	**Outcomes**
Cohort studies Case-control studies Controlled trials (with non-active control group)	Children (<18yrs) undergoing surgery	Nutritional assessment – anthropometric, biochemical	Infectious complications – e.g. blood stream infection, surgical site infection, chest infection Length of hospital stay Mortality
	Sample Search Terms		
	Child; Pre-school; Infant; Newborn; Adolescent; Young person; Surgery; Pre-operative; Post-operative; Operation; Surgery	Malnutrition/diagnosis, epidemiology, therapy; Explode nutritional assessment, nutritional status, nutritional indices; Nutritional deficiency; Protein-energy malnutrition; Dietary supplementation	Complications; Infective complications (e.g. pneumonia, bloodstream infection, urinary tract infection, sepsis); Surgical site infection (e.g. mediastinitis, endocarditis, osteomyelitis); Surgical wound infection; Bacteraemia; Central line associated bloodstream infection (CLaBSI); Infection/etiology, microbiology; Postoperative complications/etiology

2.4.1.3 Types of exposure

Any global nutritional assessment (anthropometric, biochemical or screening tool) undertaken pre-operatively with classification of nutritional status stated at the time of surgery.

2.4.1.4 Types of outcomes

Primary outcomes:

- Any postoperative infection-related complication
- Classification system used for reporting of infection-related complication

Secondary outcomes:

- Duration of follow up
- Length of stay
- Mortality

2.4.2 Search methods for identification of studies

2.4.2.1 Electronic searches

Due to the question being related to an aspect of healthcare, the bibliographic databases with a focus on medical and nursing related literature were chosen for the identification of relevant literature. Studies were identified by searching Cochrane Central Register of Controlled Trials (CENTRAL); OvidSP MEDLINE (from 1950); OvidSP EMBASE (from 1980) and NHS Evidence CINAHL (from 1982).

A word list was generated which incorporated different synonyms and phrases associated with the exposure and outcomes of interest. This included plural terms as well as singular, abbreviations and possible hyphenation. Once word lists had been generated, the lists were linked using the Boolean operators AND, OR and NOT. Truncation and wildcard functions were used as appropriate to the database being searched. Index terms were searched and exploded. The full search strategy is presented in Appendix 1. A search strategy that was sensitive for the identification of prognostic studies was adopted (Wilczynski & Haynes 2004).

2.4.2.2 Searching other sources

Literature was also identified by forward and backward citation searching of all identified papers and relevant review articles. OpenGrey and ETHos were searched in an attempt to identify relevant grey literature.

Studies were restricted to English language as no funding was available for medical translation purposes.

2.4.3 Data collection and analysis

2.4.3.1 Selection of studies

Two independent reviewers (the research student and a Consultant in Infectious Diseases) evaluated all retrieved titles and abstracts against the pre-defined inclusion criteria to identify potentially relevant studies from the search. A standardized eligibility screening form was developed for this purpose (Appendix 2).

All potentially eligible publications were retrieved in full text and independently evaluated for inclusion by these two reviewers. Disagreements were resolved through discussion, and those remaining unresolved were screened by a third reviewer (a member of the supervisory team with knowledge of systematic review methodology).

2.4.3.2 Data extraction and management

All data were extracted independently by two reviewers (the research student and Consultant in Infectious Disease) using specifically designed data extraction forms based on the Cochrane Collaboration template (Higgins et al, 2011; Appendix 2) to promote consistency and reduce bias. Disagreements were resolved through discussion with a third reviewer (a member of the supervisory team). If further clarity on content was required, attempts were made to contact study authors. When more than one published paper reported results from the same study participants, all papers were utilized to gain information relevant to this review.

The following data were extracted:

- Study design and characteristics;
- Country of origin of study;
- Type and length of surgery;
- Eligibility criteria and baseline participant data;
- Method of nutritional assessment and stratification of nutritional status;
- Outcomes including assessment method;
- Duration of follow up;
- Assessment of confounders;
- Conclusion.

2.4.3.3 Assessment of risk of bias in the included studies

Two reviewers (the research student and Consultant in Infectious Disease) independently assessed methodological quality of studies meeting the inclusion criteria using the Newcastle Ottawa Scale for Cohort and Case Control methodology (Wells et al, 2011). Disagreements were resolved through discussion with a third reviewer (a member of the supervisory team). Since observational studies are susceptible to bias mainly arising from selection of study

participants and uncontrolled confounding factors, careful evaluation of study quality was required to judge the reliability of the evidence provided within the included studies.

Since a variety of study designs were included in the review, no single quality assessment tool was suitable to assess all studies. As nutritional status was the key prognostic factor under question, assessment of study quality and risk of bias was assessed primarily using the Newcastle Ottawa Scale (NOS) which has a version for both cohort and case control studies (Appendix 3). Each version has eight items assessing three domains:

- Participant selection (representativeness);
- Comparability (due to design or analysis);
- Outcomes (assessment and follow up).

A study can receive one star (*) for meeting any one of the eight criterion, with the exception of comparability which can receive two (**). In this review, one star was allocated if age was controlled for. Two stars were allocated if there was also control for surgical case complexity.

In terms of the overall judgment of study quality, in accordance with GRADE recommendations (Guyatt et al, 2008), it was decided studies achieving four or fewer stars would be considered as providing very low-quality evidence; with studies achieving five or six considered as providing low quality evidence. Studies scoring either seven or eight stars would be considered as providing moderate quality evidence. A study would be required to achieve a maximum score of 9 stars to be judged as providing high quality evidence. It was decided *a priori* that no study would be rejected on the basis of the quality judgment, but due to the anticipated heterogeneity on a number of levels, each item considered a potential source of bias was tabulated to allow comparison between all included studies. If significant differences in quality were found to exist between studies, they would be subject to sensitivity analysis rather than using quality scores as weights in the analysis, as recommended by Stroup et al (2000).

2.4.3.4 Strategy for data synthesis

Summarizing results of studies included in the review provided an estimate of the average effect of the exposure undernutrition on outcome and investigated whether this effect is similar across studies.

Where dichotomous outcomes were reported or available (e.g. presence or absence of infection) we extracted the reported estimate of the effect which was relative risk for cohort studies, and odds ratio for case-control studies. Where estimates of effect were not reported, these estimates were calculated where possible from the reported results. These data were accompanied by 95% confidence intervals. For continuous data (e.g. length of stay) the mean difference along with 95% confidence intervals were extracted or calculated. Meta-analysis of

odds ratios or correlation coefficients would have been undertaken with testing for small study bias, but as studies demonstrated significant clinical and methodological heterogeneity in terms of participants and outcome reporting, formal pooling of results was not deemed appropriate.

In view of heterogeneity on a number of levels (study design, assessment of nutritional status, type of surgery, participant age) this review provides a best evidence synthesis rather than meta-analysis. Outcome data are presented in tabular form to guide narrative synthesis and summarize findings across included studies. For each study entry, results reported as being adjusted for during the analysis are provided. Where more than one analysis was presented in the published article, the most adjusted analysis was extracted.

2.4.3.5 Unit of analysis

Post-operative morbidity and mortality is considered a consequence of surgery if complications occur within 30 days following operation (Mangram et al, 1999). As many conditions requiring surgery in childhood are known to require re-operation, it is not unexpected that participants have more than one operation within a given study period. All studies reporting outcomes per operations performed were cohort studies. The two case-control studies included in the review (Farley et al, 2014; Nateghian et al, 2004) reported outcomes per patient, as would be expected.

For the purpose of this review, therefore, the authors have chosen to analyse and present data in the unit of analysis reported within the individual studies, recognizing that study participants may need more than one operation within the study period, and that criteria for reporting complications related to surgery is finite.

2.5 Results

2.5.1 Results of the search

The search strategy resulted in the retrieval of 1136 citations as shown in Figure 2.1, reported using PRISMA guidelines (Moher et al, 2009). Electronic database searching identified 1067 titles, of which 28 titles were duplicates and removed. The remaining 69 records were identified using backward and forward citation searching. No further studies were identified by either CENTRAL database or grey literature searching. Of the 1108 remaining citations, following independent review 1025 were discarded following examination of title and abstract. Due to the inability to determine potential eligibility by title or abstract alone, 83 studies required screening of the full text article, with 30 subsequently discarded.

Fifty-three papers progressed to eligibility screening. Following screening, two review papers and one foreign language paper were excluded. Twenty-three papers had not undertaken any form of preoperative nutritional assessment, with a further six not reporting infection complications. Five papers were undertaken in solely adult surgical populations and a further three papers potentially eligible for inclusion were found to have included participants older than 18 years of age, with the inability to extract paediatric- specific outcome data. All these papers were excluded.

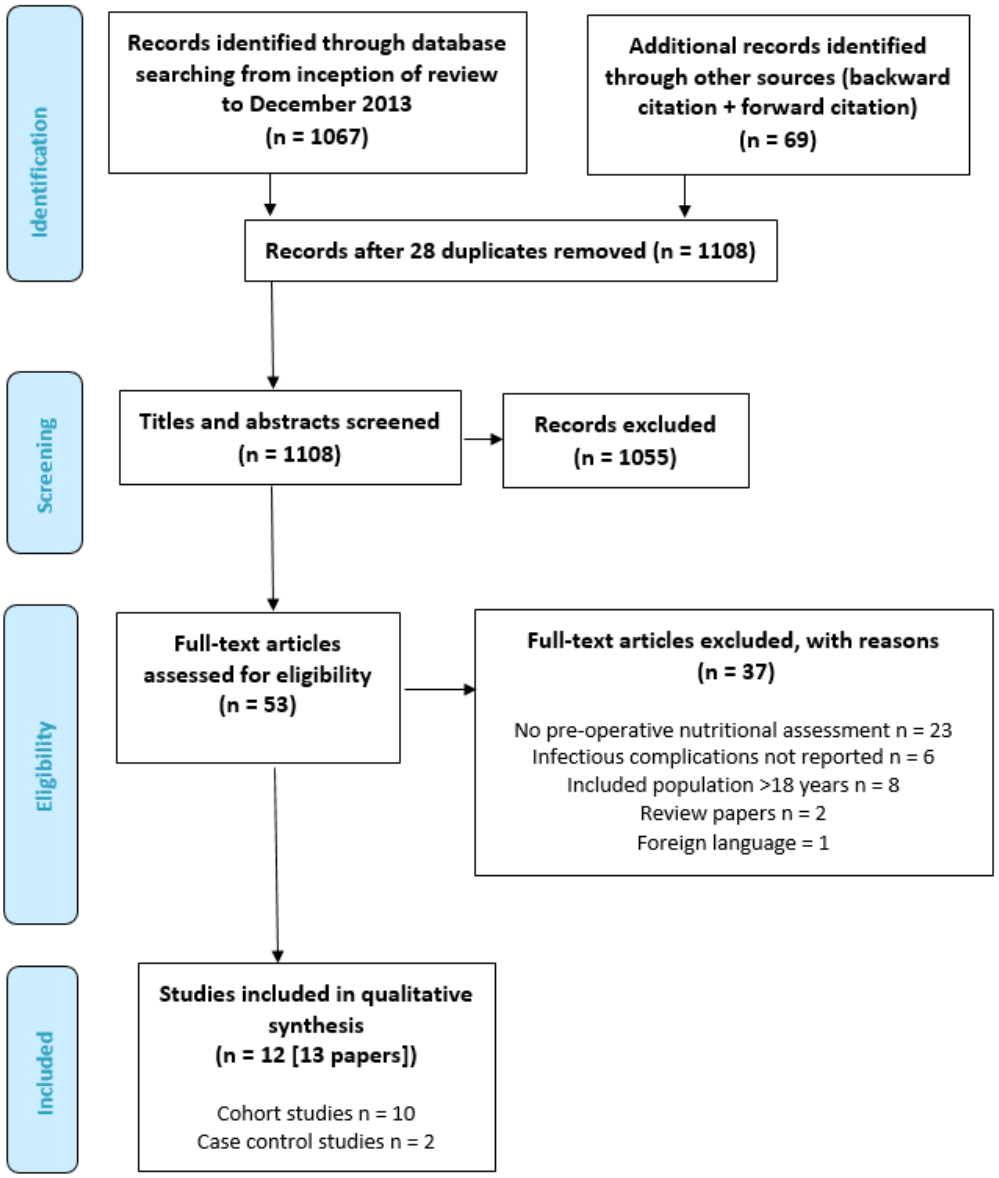
Following personal communication with one author (Leite et al, 1995; personal communication, Appendix 6) and the subsequent clarification of results not initially reported, this paper was included. Two papers from one study were identified (Bhattacharya et al, 1990; Bhattacharya et al, 1993). Data from both papers were combined for data extraction purposes. Consequently, a total of 12 studies from 13 papers were eligible for inclusion and proceeded to data extraction. Characteristics of the included studies can be viewed in Appendix 5a.

Characteristics of those studies excluded following eligibility screening, including the three papers with mixed paediatric and adult populations (Hingorani et al, 2011; Jain et al, 2007; Jevsevar & Karlin, 1993) can be viewed in Appendix 5b.

2.5.2 Included studies

Twelve studies (thirteen papers) with a sum total of 92,386 participants, fulfilled the inclusion criteria for this review. The majority of participants (n= 90,392; 98%) came from one cohort study (Stey et al, 2014), with the remaining studies between them having contributed 1,994 participants. The studies were from the USA (five studies), Canada (two studies), Mexico (two studies), South America, Thailand and Saudi Arabia (one study from each). The surgical populations represented included general surgery (four studies), cardiac surgery (four studies), and spinal surgery (2 studies). One study combined general, cardiac and neurosurgical populations, with the remaining study reporting across all surgical specialties. There were ten cohort studies and two case control studies included. Of the 92,386 participants, a total of 13,902 were classified in a category consistent with undernutrition. This gave a combined incidence of malnutrition across all studies as 15%, but when considering participants within the individual studies, over half of the studies had a burden of undernutrition assessed as being above 40%. The burden of undernutrition was most often associated with those studies undertaken in Saudi Arabia and South America, with one Canadian study reporting a 51% rate of undernutrition in a paediatric population undergoing abdominal or non-cardiac thoracic surgery.

Figure 2.1: PRISMA (2009) Flow diagram of results from search strategy and study selection



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

2.5.2.1 Participants

Two studies included participants 18 years of age or older (Hatlen et al, 2010; Farley et al, 2014). Both studies presented individual patient characteristics with outcome data that enabled these participants to be excluded from bivariate analysis, and neither study had undertaken any form of adjusted analysis. All remaining studies were carried out in children with a minimum age range reported as 3 days (Vivanco-Munoz et al, 2010) although the median age reported was 10.6 months. Three studies excluded a neonatal population: Rojratsirikul et al (2004) excluded infants less than 2 months of age, Secker & Jeejeebhoy (2007) excluded < 31 days and Stey et al (2014) excluded neonates less than 28 days due to recognition that neonatal weight is typically related to infants being large or small for gestational age, which was believed to be so complex an issue it would confound their analysis. One study reported the inclusion of 120 neonates (Bhattacharya et al, 1990/1993).

Four studies were undertaken in cardiac surgical populations (Anderson 2011; Leite 1995; Nateghian 2004; Vivanco-Munoz 2010). Five publications from four studies were in general surgical populations, mainly gastrointestinal/abdominal surgery (Al Bassam, 1994; Bhattacharyya et al, 1990; Bhattacharyya et al, 1993; Rojratsirikul et al, 2004; Secker & Jeejeebhoy, 2007). Two studies were in spinal surgical populations (Farley et al, 2014; Hatlen et al, 2010) and one study (Porras-Hernandez et al, 2003) comprised of cardiac, general and neuro surgical participants. Stey et al (2014) studied all children undergoing any type of surgery with data entered onto the American College of Surgeons National Surgery Quality Improvement Project (NSQIP) pediatric database.

2.5.2.2 Exposure

All participants had some form of nutritional assessment undertaken prior to surgery. There were a variety of methods used for nutritional assessment applied across studies. Formulae using height and weight parameters were most commonly used, with five of the retrospective studies relying on either weight-for-age Z scores (Anderson et al, 2011; Nateghian et al, 2004; Stey et al, 2014) or expected body mass index or BMI Z score calculations (Farley et al, 2014; Vivanco-Munoz et al, 2010). Prospective studies were more likely to use Waterlow's Criteria (Waterlow, 1972) based on expected weight for age and height for age (Al Bassam, 1994; Bhattacharya et al, 1990/1993; Leite et al, 1995; Porras Hernandez et al, 2003) with two studies adding some additional aspect of biochemical testing (Al Bassam, 1994; Leite et al, 1993). One study (Hatlen et al, 2010) classified nutritional status solely on levels of serum albumin with haematocrit. Two studies evaluated the efficacy of Subjective Global Assessment (SGA), a questionnaire based around nutrition related history, and compared it to objective assessment methods (anthropometric and biochemical) in their ability to predict post-

operative complications (Rojratsirikul et al, 2004; Secker & Jeejeebhoy, 2007). Please refer to Additional Tables, Appendix 8, for further details.

2.5.2.3 Potential confounders adjusted for in study analysis

Six publications from five studies did not adjust for any potential confounding variables in their analysis (Al Bassam, 1994; Bhattacharyya et al 1990; Bhattacharyya et al, 1993; Hatlen et al, 2010; Leite et al, 1995; Rojratsirikul et al, 2004). Two studies, one case-control and one cohort study, reported groups having similar baseline characteristics (Farley et al, 2014; Secker & Jeejeebhoy, 2007) with the former study reporting individual participant data. The remaining studies either matched or adjusted for age, diagnosis, surgical risk and wound class, and the remaining case study also matched on year of surgery (Nateghian et al, 2004). Three of these studies also adjusted for length of surgery (Anderson et al, 2011; Porras-Hernandez et al, 2003; Vivanco-Munoz et al, 2010) and, in addition, Vivanco Munoz et al (2010) adjusted for birth weight. One study adjusted for all the above variables except weight at birth, also adjusting for comorbidity burden and prematurity (Stey et al, 2014).

2.5.2.4 Unit of analysis issues

A number of issues were identified whilst extracting data from the included studies. Seven studies used participants as the unit of analysis in their presentation of outcome data (Anderson et al, 2011; Farley et al, 2014; Nateghian et al, 2004; Porras-Hernandez et al, 2003; Rojratsirikul et al, 2004; Stey et al, 2014; Vivanco-Munoz et al, 2010). Six publications from five studies used total number of operations as the unit of analysis (Al Bassam, 1994; Bhattacharyya et al, 1990; Bhattacharyya et al, 1993; Hatlen e al, 2010; Leite et al, 1995; Secker & Jeejeebhoy, 2007).

Four of the studies included outcomes for overweight participants in their analyses (Hatlen et al, 2010; Porras-Hernandez et al, 2003; Stey et al, 2014; Vivanco-Munoz et al, 2010). However, for the purpose of this review, only normal weight and underweight participants were included in the analysis.

2.5.3 Risk of bias in included studies

The Newcastle Ottawa Scale (NOS) was used for assessing the quality of included studies (Appendix 3). Details regarding the judgment of quality assessment is presented in Appendix 7. A visual summary of the methodological quality of included cohort studies and case-control studies separately is presented (Table 2.2 and Table 2.3 respectively). The domains of study quality assessed within the Newcastle Ottawa scale are regarding participant selection, the comparability of the sample population in terms of study design and analysis, and the

ascertainment of outcome. The findings for each of these domains are summarized in the following sections.

2.5.3.1 Selection

None of the included studies were judged as meeting the criteria for representativeness of the exposed cohort. Nine of the ten cohort studies excluded participants on either age; co-morbidity; death and/or incomplete follow-up data. In addition, one study which excluded participants with genetic or other system abnormality was undertaken in a small, homogenous group of children undergoing specific cardiac surgery (Anderson et al, 2011), and was not felt to be representative of the average paediatric surgical population that the review question was addressing.

Lack of transparency regarding the number of participants excluded from all studies was also judged to introduce a potential risk of bias. Two studies reported these data (Porras-Hernandez et al, 2003; Vivanco-Munoz et al, 2010), with excluded populations accounting for 20% of the total surgical cohort. Three studies not reporting these data were felt to have small participant numbers for the stated study period (Al Bassam, 1994; Leite et al, 1995; Hatlen et al, 2010), and were judged to be at an unclear risk of bias.

Recruitment for one study from a voluntary surgical database (Stey et al, 2014) also raised concern that included participants could be from higher performing surgical units who contribute to this data collection, therefore the study could potentially be at risk of biased outcome reporting.

All cohort studies were felt to meet the criteria for selection of the non-exposed cohort. Seven met the criteria for adequate ascertainment of exposure; two studies used BMI assessment of undernutrition not validated for use in children (Hatlen et al, 2010; Vivanco-Munoz et al, 2010), with the remaining study not defining criteria used for undernutrition in sufficient detail to be able to make a judgment (Porras-Hernandez et al, 2003). Nine of the cohort studies met the criterion for the outcome not being present at the start of the study. The two publications from the remaining study did not meet the criterion as it was unclear whether participants undergoing more than one operation during the study period were free of postoperative infection at the time of reoperation (Bhattacharyya et al, 1990; Bhattacharyya et al, 1993).

Both case-control studies faced similar problems in terms of selection of cases, with definition of postoperative infection either not being sufficiently clearly defined (Farley et al, 2014) to make a clear judgment; or providing an adequate definition but not following up participants long enough to ensure all cases were captured (Nateghian et al, 2004). Both adequately met the criteria for representativeness of cases and selection and definition of controls.

Table 2.2: Methodological quality summary for cohort studies: review authors' judgments about methodological quality items for each included study

Quality domain	Comparability								
	Selection					Outcome			
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome not present at start	Comparability of cohorts	Assessment of outcome	Duration of follow-up sufficient	Adequacy of follow-up	**Overall quality of the evidence**
Al Bassam (1994)	U	*	*	*	I	*	U	U	**Very low**
Anderson (2011)	U	*	*	*	**	*	U	*	**Moderate**
Bhattacharyya (1990/1993)	U	*	*	U	I	*	U	U	**Very low**
Hatlen (2010)	U	*	U	*	U	*	*	*	**Low**
Leite (1995)	U	*	*	*	I	*	U	*	**Low**
Porras-Hernandez (2003)	U	*	U	*	*	*	U	*	**Low**
Rojratsirikul (2004)	U	*	*	*	I	*	*	*	**Low**
Secker (2007)	U	*	*	*	U	*	*	*	**Low**
Stey (2014)	U	*	*	*	**	*	U	*	**Moderate**
Vivanco-Munoz (2010)	I	*	U	*	*	*	I	*	**Low**

Key: * =Criterion met, U =Unclear, I =Inadequate

Table 2.3: Methodological quality summary for case-control studies: review authors' judgments about methodological quality items for each included study

Quality domain	Comparability								
	Selection					Exposure			
	Case definition adequate	Representativeness of the cases	Selection of the controls	Definition of controls	Comparability of cohorts	Ascertainment of exposure	Same method of ascertainment of exposure	Non-response rate	**Overall quality of the evidence**
Farley (2014)	U	*	*	*	I	I	*	*	**Low**
Nateghian (2004)	I	*	*	*	U	*	*	*	**Low**

Key: * =Criterion met, U =Unclear, I =Inadequate

2.5.3.2 Exposure (case-control)

One of the studies met all criteria for this domain (Nateghian et al, 2004). The remaining study did not meet the criterion for ascertainment of exposure (Farley et al, 2014) as BMI is not a valid indicator of undernutrition in children less than 2 years of age without being adjusted for age and sex.

2.5.3.3 Comparability

Four cohort studies adjusted or matched for age (Anderson et al, 2011; Porras-Hernandez et al, 2003; Stey et al, 2014; Vivanco-Munoz et al, 2010). In addition, two studies also adjusted or matched for case complexity (Anderson et al, 2011; Stey et al, 2014) and met both criterion in this category. The remaining six cohort studies from seven papers did not meet the criterion either due to a) no statement being provided (Al Bassam et al, 1994; Bhattacharyya et al, 1990; Bhattacharyya et al, 1993; Leite et al, 1995; Rojratsirikul et al, 2004), b) a statement of no difference being reported (Secker 2007), or c) only conducting univariate analysis (Hatlen et al, 2010).

One case-control study met one of the criteria for comparability by matching for age (Nateghian et al, 2004) but did not undertake multivariate analysis. The remaining case-control study (Farley et al, 2014) reported similar ages, but did not formally match cases and controls therefore was not judged as fulfilling comparability criteria.

2.5.3.4 Outcome (cohort)

All cohort studies had independent assessment or record linkage for the assessment of infection-related outcome, and therefore met this criterion. Length of follow-up was judged adequate in three studies (Hatlen et al, 2010; Rojratsirikul et al, 2004; Secker & Jeejeebhoy, 2007) for the outcomes relevant to this review, where duration of follow up was until or beyond postoperative day 30. Six studies did not explicitly state duration of follow-up, therefore were judged to be at an unclear risk of bias. One study (Vivanco-Munoz et al, 2010) reported a 14-day follow-up which was not deemed adequate.

2.5.3.5 Other potential sources of bias

There were four other potential sources of biases not identified within the Newcastle Ottawa Scale. In terms of the unit of analysis used, it is recognized that using number of operations (thereby including some participants more than twice) could potentially lead to 'clustering' of individual participants which if not accounted for in the analysis may lead to invalid conclusions. In the presence of clustering both between group and within group variation needs to be considered in inferential statistics and methods to estimate confidence intervals around estimates of effect. If the right techniques are not used, this may lead to p values which inappropriately suggest significance, or confidence intervals which are too narrow leading to erroneous interpretation of the results.

More than half the included studies had sample sizes fewer than 100 (Al Bassam, 1994; Anderson et al, 2011; Farley et al, 2014; Hatlen et al, 2010; Leite et al, 1995; Nateghian et al, 2004; Rojratsirikul et al, 2004). Although sample size is more likely to contribute to lack of precision rather than contributing to a potential source of bias in these types of studies. Only one study provided a power calculation which showed that the study had an 80% chance of detecting an odds ratio of 2.1, or a 50% chance of 1.5 (Farley et al, 2014).

In terms of funding, one study received a departmental grant (Farley et al, 2014) whilst one study author was in receipt of a Doctoral research award (Secker & Jeejeebhoy, 2007). One study acknowledged support from a diagnostics company whose products enabled the measurement of serum proteins (Leite et al, 1995). None of these were deemed to be a potential source of sponsorship bias. Two studies reported nothing to declare (Hatlen et al, 2010; Stey et al, 2014) whilst the remaining studies did not mention funding. No study declared a conflict of interest.

The reported incidence of undernutrition was greater than 50% in four of the included studies (Al Bassam, 1994; Leite et al, 1995; Secker et al, 2007; Vivanco-Munoz et al, 2010). The lowest rate was found in the largest cohort study conducted in the USA, which reported an incidence

of 14.5% (Stey et al, 2014). This therefore brought the overall incidence of undernutrition across all studies to 15%. The two studies in spinal surgical populations, also conducted in the USA, reported between a third and a quarter of their participants were under-nourished. Both studies described participants according to their lowest level of neurological functioning (Hatlen et al, 2010) or according to ambulatory status and continence (Farley et al, 2014). Both of these factors could be associated with poorer nutritional status than other surgical populations.

2.5.4 Outcomes relevant to this review

A descriptive summary of relevant outcomes is provided below. Please refer to Appendix 8c: Summary of findings for further details. The review included twelve studies (13 papers) which reported post-operative infection-related complications, three of which, in addition, reported hospital length of stay according to exposure group. In all studies nutritional status was considered as a potential risk factor for infection. There was a combined total of 92,386 participants; 13,902 of which were assessed as being under-nourished by a variety of assessment methods. Due to significant clinical and methodological heterogeneity, meta-analysis was not appropriate. Mortality, where reported, was independent of nutritional status and infection related complications, therefore the decision was made to remove it from outcome analysis. A summary of mortality reporting can be found in additional tables (Appendix 8a).

Two studies compared a nutrition history questionnaire undertaken pre-operatively – the Subjective Global Assessment (SGA) - against traditionally accepted anthropometric assessments to assess the efficacy of the tool in identifying children at risk of post-operative complications (Rojratsirikul et al, 2004; Secker & Jeejeebhoy, 2007). The focus of these studies were to identify and compare undernourished children with their well-nourished counterparts; outcome data could be extracted for both groups. However, both studies provided unadjusted results from bivariate analysis, and had made little or no adjustment for potential confounding variables.

In addition to the two studies using questionnaire-based assessment, eight publications from seven studies used anthropometric assessments of nutritional status (Anderson et al, 2011; Bhattacharyya et al, 1990; Bhattacharyya et al, 1993; Farley et al, 2014; Nateghian et al, 2004; Porras-Hernandez et al, 2003; Stey et al, 2014; Vivanco-Munoz et al, 2010). Within these studies the parameters used for assessment were weight alone, weight for height/weight for age or body mass index calculations. Two studies used one of the above with a measurement of triceps skin fold to estimate subcutaneous fat with biochemical testing which included

serum albumin concentration (Al Bassam, 1994; Leite et al, 1995). One study solely used biochemical assessment markers of serum albumin and haematocrit (Hatlen et al, 2010).

All studies provided outcome data for children less than 18 years of age following surgery. Four publications from three studies included a neonatal population (Bhattacharyya et al, 1990; Bhattacharyya et al, 1993; Nateghian et al, 2004; Vivanco-Munoz et al, 2010). The number of neonates were specified in three publications from two of the studies (Bhattacharyya et al, 1990; Bhattacharyya et al, 1993; Nateghian et al, 2004) and equaled 144 neonates. The remaining two studies had an undetermined number of neonates included, with Vivanco-Munoz et al (2010) reporting 129 participants under 1 year of age, with a median age of 10.6 months (range 3 days to 36 months), and the remaining study providing only a median age of 27.5 months with no detail on range (Porras-Hernandez et al, 2003). Consequently, the number of neonates represented within these studies was extremely low.

As postoperative outcome was the variable under investigation within these studies, comparisons were reported between outcome group rather than exposure group. Since undernutrition as a variable was considered a potential risk factor, data were extracted according to nutritional status and unadjusted risk was calculated. Duration of follow-up was also extracted in order to determine ascertainment of infection-related outcome, with a minimum duration of 30 days after surgery defined as being adequate for this purpose in line with most surveillance protocols (Horan et al, 2008; PHE, 2013).

2.5.4.1 Effects of undernutrition on infection-related complications

Data were able to be extracted from the included studies for the outcomes surgical site infection (Bhattacharyya et al, 1990; Farley et al, 2014; Hatlen et al, 2010; Nateghian et al, 2004; Porras-Hernandez et al, 2003; Stey et al, 2014); pneumonia (Al Bassam, 1994; Bhattacharyya et al, 1993; Stey et al, 2014; Vivanco-Munoz et al, 2010); septicaemia (Bhattacharyya et al, 1993); and combined postoperative infection (Anderson et al, 2011; Leite et al, 1995; Rojratsirikul et al, 2004; Secker & Jeejeebhoy, 2007; Vivanco-Munoz et al, 2010). Results can be viewed in Table 2.4.

One study reported outcome data for surgical site infection, pneumonia, septicaemia and urinary tract infection (Bhattacharya et al, 1990/1993). Four studies presented outcome data for surgical site infection only (Farley et al, 2014; Hatlen et al, 2010; Nateghian et al, 2004; Porras-Hernandez et al, 2003). One study reported pneumonia only, as no other infection-related outcome occurred during the study period (Al Bassam, 1994). One study reported combined infection-related complication data and, in addition, incidence of pneumonia in those participants receiving mechanical ventilation for longer than 48-hours (Vivanco-Munoz

et al, 2010). In addition, one study also reported unadjusted results for pneumonia and urinary tract infection which contributed to composite postoperative morbidity on adjusted analysis (Stey et al, 2014) along with surgical site infection as a separate outcome measure. The remaining studies presented combined infection-related complication data (Anderson et al, 2011; Leite et al, 1995; Rojratsirikul et al, 2004; Secker & Jeejeebhoy, 2007).

2.5.4.1.1 Site Infection (SSI)

Six studies reported outcomes for surgical site infection ranging in quality from moderate to very low. Definitions used for the identification of this outcome were consistent across five of the six studies and used American Center for Disease Control criteria (Mangram et al, 1999). The remaining study (Bhattacharyya 1990) used an ASEPSIS score >21 (Wilson et al, 1986).

One study (Stey et al, 2014) performed multivariate analysis adjusting for case complexity and comorbidity burden but did not demonstrate an association between undernutrition and surgical site infection (OR 0.89, 95% CI, 1.18 – 1.5), although on univariate analysis an association was suggested. This study also reported outcome data for pneumonia and urinary tract infection which were statistically significant on univariate analysis (RR 2.69, 95% CI, 2.1 – 3.4; RR 1.89, 95% CI, 1.5 – 2.2 respectively).

No other study performed multivariate testing for SSI outcome but, on reported or calculated univariate results, relative risks were found to be greater than 1 in the three studies judged to be of low quality (Farley et al, 2014; Hatlen et al, 2010; Nateghian et al, 2004), but only one study demonstrated confidence intervals which suggested statistical significance (Hatlen et al, 2010). The remaining two studies, both judged as being of very low quality, did not demonstrate any association.

Table 2.4: Effect of undernutrition on infection-related complications (results are grouped according to outcome, and ordered by quality of the evidence

Outcome	Study	n	Relative risk (95% CI)	Odds ratio (95% CI)	Risk difference (95% CI)	Study Quality
Any infection (combined)	Anderson (2011)	55	3.6 (1.2 – 11.1)*	8.7 (1.5 – 48.6)**		Moderate
	Leite (1995)	50			0.21 (0.1 – 0.3)*	Low
	Rojratsirikul (2004)	78			0.3 (0.1 – 0.5)*	Low
	Secker (2007)	175	1.5 (1.0 – 2.3)*			Low
	Vivanco-Munoz (2010)	276	0.86 (0.5 -1.4)**			Low
Surgical site infection (Cohort studies)	Stey (2014)	80,743	1.3 (1.2 – 1.5)*	0.9 (0.8 – 1.0)**		Moderate
	Hatlen (2010)	69	3.4 (1.5 – 7.5)*			Low
	Porras-Hernandez (2003)	403	0.7 (0.4 – 1.2)**			Low
	Bhattacharyya (1990)	615	1.1 (0.38 – 3.0)*			Very low
Surgical site infection (Case-control studies)	Farley (2014)	54		2.1 (0.61 – 7.3)*		Low
	Nateghian (2004)	76		2.1 (0.65 – 6.8)**		Low
Pneumonia	Stey (2014)	80,743	2.7 (2.1 – 3.4)*			Moderate
	Vivanco-Munoz (2010)	256	0.68 (0.32 – 1.2)**			Low
	Al Bassam (1994)	74			0.1 (0.01 – 0.2)*	Very low
	Bhattacharyya (1993)	615	10.1 (2.2 – 47.3)*			Very low
Septicaemia	Bhattacharyya (1993)	615	6.3 (2.0 – 19.9)*			Very low
Urinary tract infection	Stey (2014)	80,743	1.8 (1.5 – 2.2)*			Moderate
	Bhattacharyya (1990)	615	10.1 (1.1 – 90.1)*			Very low

*=calculated;**=reported. For risk difference, values >0 denote an increased risk of infection for undernutrition (0=no difference in infection risk).

2.5.4.1.2 Combined postoperative infection-related complications

Five studies of moderate and low-quality evidence reported an outcome for combined infection-related complications. One study in a cardiac surgical population (Anderson et al, 2011) of moderate quality, reported an odds ratio of 8.7 (95% CI, 1.5 – 48.6, p = 0.006) following adjusted analysis, and one study of low quality also had a relative risk suggestive of an association between undernutrition and infection (RR 1.5, 95% CI 1.0 – 2.3, Secker & Jeejeebhoy, 2007). Two further studies, judged to be of low quality of evidence (Leite et al, 1995; Rojratsirikul et al, 2004) had no episodes of infection in their normally nourished groups, therefore relative risk could not be estimated. Consequently, the risk difference was calculated for these studies (Table 2.4). Both studies demonstrated an increased risk of infection for children with undernutrition, compared to those with normal nutritional status (0.21 and 0.3 respectively). One study, also of low quality, did not find an association (Vivanco-Munoz et al, 2010) but confidence interval included 1.

2.5.4.1.3 Other infection-related complication outcomes reported

Outcome data for pneumonia were presented in four studies which all reported unadjusted risk estimates. One moderate quality study (Stey et al, 2014) reported a relative risk of infection in their undernourished group as 2.69 (95% CI, 2.13 – 3.41). One study of low quality did not find an association, but confidence intervals included 1 consistent with no significance (Vivanco-Munoz et al, 2010). Two very low-quality studies also reported data for this outcome, neither providing meaningful data to enable interpretation (Al Bassam, 1994; Bhattacharyya et al, 1993).

Stey et al (2014) reported unadjusted results for postoperative urinary tract infection demonstrating an association which was statistically significant (RR 1.84 (95% CI, 1.5 – 2.2). In addition, Bhattacharyya et al (1993), a study of very low quality, had a calculated relative risk for septicaemia of 6.34 (95% CI, 2.0 – 19.9), which although confidence intervals do not include 1 the lack of precision makes drawing a conclusion difficult. No other studies reported individual infection complications.

2.5.4.2 Effects of undernutrition on postoperative length of stay

Data regarding length of stay were extracted from three studies (Anderson et al, 2011; Rojratsirikul et al, 2004; Secker & Jeejeebhoy, 2007). One study looked at overall hospital length of stay (Anderson et al, 2011), whilst the remaining two studies looked at postoperative length of stay (Rojratsirikul et al, 2004; Secker & Jeejeebhoy, 2007). Findings are summarized below in Table 2.5. All three studies found undernutrition to be associated with a longer length of hospital stay, and this association achieved statistical significance in all studies.

Table 2.5: Effect of undernutrition on postoperative length of stay (ordered according to quality of evidence)

Length of stay (LOS) in days	Study	n	Statistical method	Effect size	Quality of the evidence
Hospital LOS	Anderson (2011)	55	Median difference	3.5*, *p*= 0.06**	Moderate
Postoperative LOS	Rojratsirikul (2004)	78	Median difference	7.5*, *p*= 0.01*	Low
	Secker (2007)	175	Mean difference	2.9**, 95% CI (0.52 - 5.3)*	Low

*=calculated, **=reported

2.6 Discussion

2.6.1 Summary of main results

2.6.1.1 Surgical site infection

Six studies reported surgical site infection. The best quality of evidence was provided by one study (Stey et al, 2014). This study was well-powered, used a heterogeneous surgical population and investigated whether extreme outliers of weight percentile experienced more postoperative complications. A secondary outcome was surgical site infection, and although significant on univariate analysis, following adjustment for confounding variables of case complexity, age and co-morbidity burden, undernutrition was not found to be significantly associated with surgical site infection. Additionally, as all participants were identified from a voluntary surgical database this may have introduced an element of selection bias in terms of the type of institutions providing data.

One study was in a small (n= 55), extremely homogeneous population undergoing cardiac surgery (Anderson et al, 2011). A relationship between undernutrition (as classified by low weight-for-age z-scores) and serious infection-related complications achieved statistical significance in both unadjusted and adjusted analyses.

As neonates are represented at low numbers there is currently no evidence available in this age group to determine if a relationship exists between undernutrition and surgical site infection.

In summary, there is evidence to suggest that there is no association between undernutrition and surgical site infection in young children, but evidence is lacking to determine this relationship in neonatal surgical populations.

2.6.1.2 Other infection-related complications

Five studies reported a combined rate of postoperative infection-related complications. Two of these studies had no incidence of infection in the normal groups. Stey et al (2014) reported outcome data for pneumonia and urinary tract infection which achieved statistical significance on univariate analysis, however, composite infection complication data were not reported for these outcomes which presented a potential risk of bias in terms of selective outcome reporting. Following unadjusted analysis three of the remaining studies all provided low quality evidence and demonstrated relative risks greater than 1 in the undernourished groups (Farley et al, 2014; Hatlen et al, 2010; Nateghian et al, 2004), but only one study demonstrated confidence intervals which were of statistical significance (Hatlen et al, 2010). The remaining study failed to demonstrate a relationship (Vivanco-Munoz et al, 2010) but had an infection outcome which comprised of only three diagnoses – pneumonia, mediastinitis and septicaemia, with a duration of follow-up as inadequate to be certain all cases would have been identified. However, again, due to the lack of neonates in the review, the evidence in this age group is lacking.

Overall, outside of a neonatal population, there is tentative evidence to suggest a relationship between undernutrition and infection-related complications.

Where infection-related complications were reported individually (pneumonia, urinary tract infection and septicaemia) results suggested a relationship between undernutrition and increased risk of infection, but analysis was unadjusted for other factors which may have been influencing this effect. In addition, due to the wide confidence intervals seen in the results from one of these studies, despite not including 1, it is difficult to draw strong conclusions with this degree of imprecision.

There is insufficient evidence to make a judgment regarding the association between undernutrition and the individually reported complications of pneumonia and septicaemia. There is tentative evidence to suggest there may be an association between undernutrition and postoperative urinary tract infection.

2.6.1.3 Infection-related complications in cardiac surgical populations

Four studies reported infection-related outcomes for a purely cardiac surgical population (Anderson et al, 2011; Leite et al, 1995; Nateghian et al, 2004; Vivanco-Munoz et al, 2010). The total number of children undergoing surgery in these studies amounted to n= 457, with a combined incidence of malnutrition at 49% (n= 225). One of these studies reported surgical site infection alone (Nateghian et al, 2004) whilst the remainder reported combined infection-related complications. Two studies (Anderson et al, 20111; Nateghian et al, 2004) had odds

ratios greater than 1 (OR 8.7; OR 2.1 respectively) although only the former study, following the adjusted analysis, had confidence intervals which did not include 1. One of the remaining studies, Leite et al (1995), had no incidence of infection in their normally nourished group, therefore the direction and size of effect was calculated using risk difference, which demonstrated a 0.21 increase in the risk of infection with undernutrition compared to those normally nourished. The final study (Vivanco-Munoz et al, 2010) was the only one which did not demonstrate an increased risk of infection with a relative risk of 0.89 (CI, 0.46 – 1.44). Although this was the largest single study (n= 276), the nosocomial infection-complications reported were limited to pneumonia, mediastinitis and sepsis, therefore not all infections were reported, making comparison with other studies difficult. Of note, mediastinitis was the only surgical site infection reported.

Apart from Anderson et al (2011) which was judged to be of moderate quality, all remaining studies were of low quality. When taken together, however, the direction of effect appears to support more of a relationship between undernutrition and infection-related complications in this surgical specialty as compared to those studies with mixed paediatric surgical populations.

2.6.1.4 Length of stay

Three studies reported a between group comparison for postoperative length of stay (Anderson et al, 2011; Rojratsirikul et al, 2004; Secker & Jeejeebhoy, 2007). The remaining studies reported length of stay for all study participants therefore data were not extracted. Due to differences in both outcome definition and the unit of measurements reported, results are not directly comparable. It is difficult to determine if undernutrition is having an independent effect on length of stay, or whether it is the association with postoperative infection-related complication that is having the effect on length of stay. For the one study undertaking adjusted analysis (Anderson et al, 2011) results suggested that although undernutrition approached significance in its relationship with length of stay (p= 0.06), the biggest effect on length of stay was seen in the presence of serious postoperative infection (p= < 0.001).

2.6.2 Overall completeness and applicability of the evidence

This review included 12 English language studies published over the last 20 years from hospital settings with the majority from North, Central and South American countries. There was a sum total of 92,386 participants, with 13,902 being classified in an undernutrition category. This gave the combined incidence of malnutrition across all studies as 15%, but considering participants within the individual studies, over half of the studies had a burden of undernutrition assessed as being above 40%. The highest levels of undernutrition, as expected,

were found in those studies carried out in South America, where the association between low income and poor growth is already known (Nandy et al, 2016), and in those surgical populations where underlying diagnosis is known to be associated with poor growth, such as congenital heart disease and abdominal pathology (Costello et al, 2015; Bethell et al, 2017; Fung, 2017).

In terms of definition of the exposure, anthropometric variables were used to define nutritional status in all but one of the studies (Hatlen et al, 2010) but various classification systems and thresholds for defining undernutrition were used. This introduced significant heterogeneity which made direct comparison across studies difficult. Weight based assessment was the most frequent method used, which is not unexpected as this is routinely measured as part of the preoperative assessment. Studies prior to the year 2000 were more frequently found to use Waterlow's criteria to classify weight, and those after were more likely to use Z scores. This most likely reflects World Health Organization (2006) recommendations to use an additional cut-off as -2 SD with which to define malnutrition.

The plethora of nutritional assessment tools and varying thresholds for defining undernutrition reflects the lack of a gold-standard nutritional measurement tool. Direct comparison between studies was thus complicated and meant formal pooling of results for estimating effect was not indicated. This finding, however, did support the findings of Joosten et al (2008) by identifying the most established way of describing undernutrition is by utilizing standard deviation scores using a defined reference population (either reference charts from the specific country, or from standard international reference charts).

Although standards for assessing the nutritional status of children are well established, debate continues over whether these criteria are suitable beyond growth monitoring of healthy children. Common anthropometric measurements of nutrition, such as weight for length, length for age, and BMI have been found to be inaccurate in children with chronic illness (Wessner & Burjonrappa, 2014). The limitations of anthropometric methods as applied to ill children have been reported, but in the absence of an established gold standard technique it continues to be widely applied as a tool for assessing nutritional status (de Souza Menezes et al, 2012). It has been identified that a uniform definition of malnutrition must be employed, and validated methods for nutritional assessment must be developed and implemented, especially for hospitalized, critically ill children (Mehta et al, 2017).

In terms of outcome definition, again, a variety of definitions and systems for classification were used across the studies. The Center for Disease Control (CDC) criteria were cited most commonly as a classification method, but variable or unclear durations of follow-up made it

difficult to determine if all studies were treating participants in a comparable way and introduced an element of uncertainty in terms of whether all true incidence of infection were captured. This finding is important, because it has been the lack of standardized nomenclature and reporting that has made precise estimates of incidence challenging (Costello et al, 2012), and in addition leads to the inability to compare results within and across surgical specialties as a quality metric. Without these robust and consistent definitions attempting to identify temporal from causal associations will be problematic.

Three studies included participants from more than one surgical specialty, with the largest cohort number from one of these studies (Stey et al, 2014). This was the only study to adjust for surgical case complexity, thus controlling for operative risk as a potential confounding variable. Neither of the two remaining studies, both judged as providing low quality evidence, adjusted for surgical case complexity, although one (Porras-Hernandez et al, 2003) did adjust for length of surgery in multivariate analysis, which could be viewed as a surrogate marker for complexity. As more complex surgery will take longer to perform, this is important as duration of operation in excess of 3 hours has been implicated as a risk factor for SSI (Procter et al, 2010; Bekelis et al, 2016).

Including multiple surgical specialties within one study, especially without attempts to control for complexity, did significantly increase clinical heterogeneity and increase the likelihood that any true effect of undernutrition on the incidence of infection-related complications would be masked. Studies including one surgical specialty were generally underpowered to detect statistically significant differences, especially when the average event rate of infection-related complications was 16% across all studies, with a range between 2% (Stey et al, 2014) and 42% (Hatlen et al, 2010).

Consequently, the applicability of the review findings are likely to be of relevance only to those single surgical specialties included. Due to the restriction of neonates from the largest, higher quality study and a general underrepresentation from the remaining included studies, evidence regarding the relationship between undernutrition and infection-related complications is severely lacking with respect to neonates aged less than 28 days.

2.6.4 Quality of the evidence

The Newcastle Ottawa Scale was used to assess the quality of the evidence. Of the twelve studies, two studies provided moderate quality evidence according to assessment with the Newcastle Ottawa Scale. Ten studies provided low quality evidence, with two studies providing very low-quality evidence. All studies reported postoperative infection-related complications, either combined or specific.

There were no studies judged as being of high quality, and only two studies were judged to be of moderate quality (Anderson et al, 2011; Stey et al, 2014).

For studies judged as low or very low in quality, downgrading the level of evidence was due in some cases to study design – most of the cohort studies had significant participant exclusions prior to study entry, others had inadequate definitions of either exposure or outcome – and in others it was due to a lack of reported information with which to make a clear judgment. The lack of high-quality data due to variations in study design and methodology used for nutritional assessment made interpretation difficult, previously reported by Wessner & Burjonrappa (2014).

Most of the studies did not provide an *a priori* power calculation, with the exception of Hatlen et al (2010), and the majority of studies in this review have small sample sizes, therefore were underpowered to detect important clinical differences. There also appears to be important methodological issues with the non-reporting of baseline characteristics in those studies not adjusting for clinical or demographic variables.

On univariate analysis, both moderate quality studies demonstrated an association between undernutrition and postoperative infection-related complications, but this was not consistent following multivariate analysis (Anderson et al, 2011; Stey et al, 2014). Two of the studies judged at low quality also demonstrated this initial association, with confidence intervals suggesting statistical significance (Secker & Jeejeebhoy, 2007; Hatlen et al, 2010). The remaining low-quality studies were equally split in terms of direction of effect, but none were able to demonstrate statistical significance.

In addition, variation in unit of analysis may result in 'clustering' which is especially pertinent in studies of small size. Clustering may potentially overestimate or underestimate the effect of malnutrition related infection complications depending on the nutritional status of those participants requiring multiple operations.

2.6.5 Strengths and limitations of the review

Only three bibliographic databases were searched, and although attempts were made to identify unpublished literature by searching online databases, it is recognized that a lack of unpublished articles may have introduced publication bias and increased the risk of a Type II error. In addition, using a search filter to identify studies regarding prognosis may have excluded controlled trials of nutritional intervention in which the control groups may have been eligible for inclusion.

Although conference proceedings were included in titles for screening generated by bibliographic searching, none were included in the review. This was primarily due to the fact

that none were judged to meet the review inclusion criteria, but review authors were also cognizant that any conference proceeding not progressing to publication would not have been through a process of peer review. In addition, foreign language studies were excluded from the review due to lack of funding which meant medical translation was not possible. One study where the abstract had been translated from Spanish into English did otherwise appear to be eligible for inclusion.

Of some concern were the number of titles retrieved from forward and backward citation searching, which could imply an ineffective search strategy. Indeed, five out of the sixteen full text articles retrieved and screened for inclusion in the review were found by this method. Another reason to explain this may be the inconsistency of MeSH terminology used within the bibliographic databases searched, and variation between databases in how articles regarding prognosis are indexed. It must also be recognized that due to the nature of the review question, all search strings were complex and crossed many diagnostic fields.

During the screening for inclusion stage, two primary authors were contacted in order to provide clarification over their reported outcomes, although both studies had been published twenty years ago. Following data extraction, it would have been necessary to contact all primary authors for further information regarding some aspect of study quality assessment, we decided decisions regarding study quality would be based upon what and how information was presented in the published paper. This may have adversely affected the quality rating of those papers where English was not the authors' first language.

Unit of analysis variations resulted in lack of standardization for data extraction purposes, which may result in the review being at risk of Type II error. Narrative synthesis makes it difficult to detect small effects due to the substantial heterogeneity between studies, thereby increasing the potential for this type of error.

The assessment of quality in observational studies has been recognized as complex and prone to bias. As this review incorporated both case-control and cohort studies, the Newcastle Ottawa Scale (Wells et al, 2011) was chosen as the preferred tool for quality assessment. However, as the nature of the review question related to prognosis, we deviated from protocol to enable the method of quality assessment to be adapted. We continued to assess quality using the NOS categories of Selection, Comparability and Outcome or Exposure (dependent on cohort or case control methodology) but we also incorporated the domains included in the framework developed by Hayden et al (2006) specifically for studies considering prognosis. This adaptation was felt to enable a more rigorous assessment of the quality of each included

study in addressing heterogeneity of both exposure and outcome measures. The reproducibility of this technique, however, has not been tested.

Three independent reviewers were involved in the identification and screening of studies, and in the data extraction process. This process adds robustness to the process and reduces bias therefore is an advantage over a traditional narrative review of the literature. In addition, the methodological quality of included studies is assessed which allows a decision to be made as to the robustness of the evidence, by determining if methodological bias may have affected the results. In addition, as all surgical populations were included, this increases the generalizability of study findings to other paediatric surgical populations.

2.7 Conclusion

2.7.1 Implications for practice

There is inadequate evidence to draw strong conclusions from the review findings. Associations between undernutrition and infection-related complications were often inconsistent between studies. This is in part due to the heterogeneity of the sample population but may also reflect the plethora of nutritional assessment methods assessing undernutrition, and the varied outcome definitions used across the included studies. Despite this, there appears to be tentative evidence from one of the moderate quality studies (Anderson et al, 2011) to suggest there may be a relationship between undernutrition and all infection complications when considered together, but less evidence to support an association when individual infection complications are investigated (Stey et al, 2014).

As infection-related complications are infrequent events included studies were underpowered to detect statistically significant results. Infection complications after surgery are recognized as being multifactorial, and the majority of these were limited by small sample sizes which would consequently limit adjustment for potential confounders within study design.

Due to the lack of included neonates within the review, there is an absence of evidence for this age group with which to assess the potential relationship between undernutrition and infection-related outcomes.

2.7.2 Implications for future research

In order to answer the question of this review large, adequately powered prospective studies are required which should include a gold-standard method of nutritional assessment and agreed definitions of undernutrition in order to facilitate the investigation of the impact of undernutrition on clinical outcome. The wide variation in assessment methods used is likely to be reflective of the retrospective design of most studies and the necessity of using primarily

weight-based data, and the technique most favored during the time period the study was undertaken. Perhaps, of more concern, it may be reflective that despite the recognized importance of measuring and plotting child development and growth, the interpretive value of these data in clinical practice may be inadequate. Indeed, there appears to be agreement in more recently published literature that although recognizing malnutrition is important, particularly in hospitalized children recognized as being at increased risk, persisting evidence exists that it is being poorly integrated into practice (Hartman et al, 2012; Wisken et al, 2012). This may also account for studies recently published focusing on methods for nutritional screening, rather than on clinical outcome (Gerasimidis et al, 2011; Hulst et al, 2010; Pichler et al, 2014; Wong et al, 2012).

To answer the question of this review, future research needs to make a distinction between viewing undernutrition as a potential prognostic factor for infection, or it being explored as a potential risk factor for infection outcome. In this way, studies can be adequately powered to detect statistical significance, and a measure of nutritional status included in multivariate analyses of potential confounders on outcome. Retrospective analyses based on database entries, although providing excellent power, will be inherently prone to selection bias depending on whether data submission is optional or compulsory; and, if not anonymized, issues of performance are likely to make them prone to selective outcome reporting. Definitions for infection-related complications also need to be more robust and applied consistently across any future studies looking at postoperative outcome.

Findings are of particular relevance to patient populations with chronic disease where growth failure has already been recognized (Joosten & Hulst, 2008; Pawellek et al, 2008), and who as part of their disease management will require surgical intervention. Especially pertinent are those surgical specialties where patients will be critically ill postoperatively, and it is anticipated they will require a proportion of their recovery time within an intensive care environment. It is these patient populations who are likely to be most vulnerable to postoperative complications as a consequence of undernutrition, in addition to being most vulnerable to further nutritional depletion during their inpatient stay.

2.7.3 Closing summary

From the existing body of published evidence, the review question remains unanswered. Although low quality evidence was found suggesting undernutrition may be predictive of postoperative infection complications in children, there was little evidence regarding a relationship with surgical site infection. However, inconsistencies in nutritional and outcome assessments made drawing conclusions difficult. The direction of effect appeared to be stronger when only considering studies undertaken in paediatric cardiac surgical populations.

Although the overall quality of the evidence remained low, it did include one of only two moderate quality studies. Small sample sizes limit the interpretation of this finding, but this potential relationship certainly warrants further investigation especially within a surgical population already known to be at nutritional risk, and where the majority of corrective and palliative surgery is undertaken in children less than one year of age, including a high proportion of neonatal surgery. As identified by this review, this is an age group which has been seriously underrepresented in the existing research.

Findings support the importance of the research question, and the suggested relationship should be investigated further. Since paediatric cardiac surgical populations formed part of the evidence, there is justification for looking further at this patient group. The incidence of surgical site infection in the review, where reported, was low therefore the included studies may have been underpowered to detect significant statistical or clinical differences. In addition, the exclusion or low numbers of neonates may have confounded individual study findings. Definitions for infectious complications need to be robustly defined and consistently applied in future studies looking at postoperative infection related outcomes.

Chapter Three: Investigating nutritional status as a risk factor for surgical site infection in children undergoing surgery for congenital heart disease

3.1 Introduction

Study 1 explored the relationship between undernutrition in children undergoing surgery and postoperative infection-related complications. Following a systematic search of the literature, 12 studies were identified and reviewed. The review concluded that in children there was tentative evidence for undernutrition being prognostic of infective complications but with little evidence to suggest an association when surgical site infection (SSI) was considered alone. In the analysis of those studies undertaken in children undergoing cardiac surgery the evidence, although weak, was more suggestive of this relationship, with three of the four studies showing a direction of effect suggesting an increased risk of infection in those who were underweight. However, the review was limited by the varying definitions used relating both to the exposure and outcome classification between studies, and by the underrepresentation of neonatal surgical populations, therefore conclusive evidence was not obtained.

With surgical site infection in a paediatric cardiac surgical population being the main focus of interest underpinning the research important questions remained unanswered. As neonates account for almost a third of the annual paedatric cardiac surgical workload the evidence in this age group was severely lacking. Additionally, there was a suggestion from review findings that incidence of postoperative infection in those studies undertaken in a cardiac surgical specialty was higher than for other specialties (with the one exception of bowel-related general surgery). Consequently, further exploring risk in this specific surgical population was justified.

In this study, Study 2, the potential link between undernutrition and SSI in children undergoing paediatric cardiac surgery (PCS) is explored. Although all postoperative infections would ideally have been studied, this would have required a prospective study, as robust outcome data was only available for SSI due to a cardiac surveillance system which had been put in place. With the availability of a historical, validated SSI dataset within an existing paediatric cardiac surgical database, it was feasible to study SSI within this population and investigate whether undernutrition was independently associated with postoperative infection.

Children with congenital heart disease are reported to be at high risk of undernutrition due to their cardiac pathophysiology and, specifically, SSI is one of the more common infection complications following surgery in this subgroup. Consequently, from the wider perspective of

the systematic review, the focus in this study narrows to one specific type of healthcare-associated infection, that is SSI, in the specific subgroup of paediatric cardiac surgery.

In the hospital where this study took place ongoing prospective surveillance of SSI in children undergoing congenital heart surgery has occurred since 2010, using the Centre for Disease Control (CDC) methodology (see Appendix 9). This enabled robust case identification for the purposes of the chosen study methodology using analysis of retrospective data.

This chapter commences with a review of the current literature with particular reference to the nutritional challenges experienced by children undergoing surgery for congenital heart disease, with a review of SSI aetiology presented. This is followed by the presentation of the research study exploring whether undernutrition is an independent risk factor for SSI complications, when controlling for other known or likely risk factors, for children undergoing PCS. Although the initial research question was to determine the prevalence and relationship of undernutrition with SSI for all age groups undergoing surgery, an additional question of interest with respect to the neonatal population emerged during the analysis, and this will be presented as a subsidiary analysis.

3.2 Background

Nutrition in paediatric surgical patients is essential not only for maintaining growth but also to promote healing and the return of organ tissue function during periods of critical illness. There is evidence that many children admitted to paediatric intensive care units (PICU) may not receive adequate calorific intake during their admission (Ngo et al, 2001; Kyle et al, 2012; Mehta et al, 2012).

The paediatric congenital heart population will spend varying time within a PICU environment after their surgery as part of routine postoperative management, where the provision of adequate nutrition is further compromised by an additional burden placed by strict regimens of post-operative fluid restriction following cardiac surgery. In addition, the further interruption of feeding for additional therapeutic procedures required after initial operation (for example, chest drain removal), will further prolong the time before full enteral feeding can be established.

As previously identified from Study 1 undernutrition in children is being assessed in a variety of ways. WHO guidelines define severe acute malnutrition as a weight for height *z*-score of less than -3 or a mid-upper arm circumference of less than 115mm (Ashworth et al, 2004). However, none of the studies included in the systematic review used height-based anthropometric definitions, instead using weight-based or BMI based criteria, which is likely

reflective of the use of body weight for drug-related calculations in children undergoing surgery (Hill et al, 2016).

There is evidence of a relationship between low weight-for-age z (WAZ) scores and increased postoperative morbidity in children with cardiac disease; Mitting et al (2015) found longer duration of postoperative mechanical ventilation and longer intensive care stay, with higher rates of late mortality. Eskedal et al (2008) have also reported higher rates of late death with low WAZ scores following cardiac surgery. Infection-related adverse outcomes were not included as outcomes in these studies. To date, any relationship between undernutrition and infection risk has not been reliably established and, therefore, warrants further investigation. This is important because if poor nutrition is found to be associated with increased postoperative infection, there is an opportunity for this to be targeted in the preoperative period and represents a potentially modifiable risk factor.

3.2.1 Aetiology of SSI

According to an English national survey, surgical site infection (SSI) accounts for at least 15.7% of all healthcare associated infection (Health Protection Agency, 2011). SSI is an infection that develops within 30 days following an operation or within one year if an implant is placed at the time of surgery and the infection appears associated with it (Horan et al, 2008). An implant is defined as a non-human foreign body that is placed permanently in the patient during an operation. In congenital heart disease, examples are prosthetic heart valves, sternal wires, and valved or non-valved conduits left permanently in situ. SSI has been shown to comprise up to 16% of all healthcare-associated infections (PHE, 2013).

SSI can either be caused by endogenous or exogenous contamination of an incision with microorganisms. Most SSIs are considered as preventable if appropriate care measures are taken to reduce the risk of infection. Evidence from adult settings shows use of a surveillance framework can result in reductions in the numbers of SSI (Geubbels et al, 2004; Rioux et al, 2007).

The development of a wound infection depends on the complex interplay of many factors. When the integrity and protective function of the skin is breached large quantities of different cell types enter the wound and initiate an inflammatory response. This may be characterised by the classic signs of redness, pain, swelling, raised temperature and fever (Calvin, 1998). Surgical wounds have the potential for bacterial invasion which will compete with the patient's own body defences, and early studies have shown the dose of bacterial contamination at operation is the chief determinant of wound infection (Cruse, 1970; Raahave et al, 1986).

The potential for infection will depend on patient specific variables such as younger age, the length and location of hospital stay (Taylor & Shekerdemian, 2016) as well as the state of hydration, nutrition and existing medical conditions (Percival, 2014). In addition, extrinsic factors related to pre, intra-, and postoperative care – for example, timing of antibiotic prophylaxis – may also influence SSI risk and this interplay of factors often makes it difficult to predict which wounds will become infected (Heinzelmann et al, 2002). These will be discussed in the next section.

3.2.2 SSI prevention strategies

Randomized controlled trials demonstrating direct cause-and-effect relationships regarding specific interventions for successfully reducing SSI are scarce, and although surgery specific and generic risk factors have been postulated within the literature, there is a paucity of high-level scientific evidence that their modification effectively reduces SSI risk (Smith, 2012; Gibbons et al, 2011). Nevertheless, clinical recommendations have been developed for SSI prevention (NICE, 2008), embedding the concept of primary prevention as a management objective for all healthcare practitioners.

It is generally accepted that SSI risk is influenced by the characteristics of the patient, the operation and aspects of postoperative care (Gibbons et al, 2011). This has led to the popularity of standardising aspects of clinical care as a prevention strategy, particularly for healthcare acquired infection, promoting consistency in the provision of care to all patients all of the time. This is termed a 'care bundle approach', which is a preventative approach of packaging best, evidence-based measures into routine care for all patients (Leaper et al 2014). Care bundles have been reported to lead to reductions in SSI risk (Stuhlberg et al, 2010; Izquierdo-Blasco et al, 2015) and the methodology has been promoted in the UK for SSI prevention purposes, as advocated by Department of Health (2011) guidelines which include preoperative stages including screening and decolonization for MRSA, preoperative showering, and hair removal using clippers not shaving; intraoperative stages including use of alcoholic skin preparation, prophylactic antibiotic use, normothermia, impregnated incise drapes, supplemental oxygen therapy and normoglycaemia; and postoperative stages including leaving wound dressing undisturbed for 48-hours, and correct hand hygiene procedures before and after each episode of patient contact.

Paradoxically, although the implementation of a care bundle approach has led in some instances to a reduction in SSI rates, there remains little evidence to conclude that the specific interventions included will independently lead to SSI reduction. However, it has been recognised that the increased scrutiny inherent when measuring performance (i.e. compliance monitoring) at the point of care delivery may result in positive changes due to the Hawthorne

effect, whereby an aspect of an individual's behaviour is modified by their awareness of being observed (Holden, 2001). Additionally, the feedback of SSI rates to individuals involved in the care of surgical patients which is part of the bundle process may act as a strong impetus for improvement, as identified by Ivers et al (2012) in a systematic review assessing the effects of audit and feedback on professional practice and healthcare outcomes. Their findings suggest this is an effective method in improving professional practice, with larger effects seen when baseline performance is low, but effectiveness can be dependent on the source and nature of feedback mechanisms. Improvement is more likely, therefore, when provided by supervisors or senior colleagues.

It must also be recognised that it may be difficult to disentangle the effect of the bundle versus changes in surgical technique over time (e.g., reduction in use of delayed sternal closure, reduction in use of implantable material, changes in surgical staff). The multi-factorial nature of SSI development is recognised as making it difficult to predict SSI risk in an adult population, where there has been more investigation than within paediatrics (Graf et al, 2009; Thompson et al, 2011). Certainly, there is acknowledgement that there may be patient, surgical and other factors that may not be modifiable.

3.2.3 Surgical site infection risk in children undergoing congenital cardiac surgery

Reported rates of SSI following cardiac surgery vary within the paediatric literature. Of note, there are currently no published UK data regarding SSI rate following paediatric cardiac surgery. Rates in studies from other parts of the world vary depending on the classification method of SSI being reported. Naturally, having an appropriate definition which is consistently applied during a pre-defined follow-up, is a necessary condition for any observed percentage of wounds classified as infected to be valid and comparable across centres (Gibbons et al, 2011). Prior to Gibbons et al's work investigating the robustness of four commonly used definitions in clinical practice, namely, CDC (Horan et al, 1992), NINSS modification of CDC (Wilson et al, 2002), presence of pus, and ASEPSIS (Wilson et al, 1986) there had been little or no critical evaluation of either the original or modified CDC definitions. Previous work determined that CDC criteria was by far the most commonly applied SSI definition with 42% of the included studies using it for classification purposes (Hill et al, 2016). With this caveat, extrapolated paediatric cardiac SSI rates from published studies range between 2.3% and 7.8% (Allpress et al, 2004; Levy et al, 2003).

In addition to definitional variation, methodological differences within these studies make direct comparisons regarding risk factors and rates difficult; some studies investigate SSI risk alone (Adler et al, 2012; Allpress et al, 2004; Nateghian et al, 2004; Kagan et al, 2007;

Holzmann-Pazgal et al, 2008; Ben Ami et al, 2008; Costello et al, 2010; Harder et al, 2013; Sohn et al, 2010; Shin et al, 2011). In contrast, many other studies investigate overall risk for healthcare-associated infection (Algra et al, 2012; Mehta et al, 2010; Sarvikivi et al, 2008; Levy et al, 2003; Rosanova et al, 2009; Barker et al, 2010; Valera et al, 2001; Pollack et al, 2010; Dagan et al, 2011). In studies exclusively investigating SSI, independent risk factors appear to be consistently reported; age less than one month (Allpress et al, 2004; Sarvikivi et al, 2008; Ben-Ami et al, 2008; Sohn et al, 2010) or age less than one year depending on categorical cut-offs (Barker et al, 2010; Costello et al, 2010) are the most commonly reported. Duration of surgery has also been reported frequently as an independent risk factor for SSI (Allpress et al, 2004; Nateghian et al, 2004; Costello et al, 2010; Adler et al, 2012), with both studies by Costello et al and Adler et al also including RACHS operative risk stratification as a measure of case complexity. Sarvikivi et al (2008) and Barker et al (2010), however, reported a longer duration of preoperative stay as being a better predictor of SSI than actual duration of surgery. Of clinical relevance prior to developing this study, only one of these prior studies had included some form of nutritional classification (Nateghian et al, 2004), and although there appears to be consistency in the risk factors being reported across studies, they are limited in their clinical relevance because most are not modifiable.

In adult surgical populations preoperative nutritional status has been more extensively studied as a strategy to reduce postoperative morbidity, including infection. Hubner et al (2012) randomized 152 adults undergoing gastrointestinal surgery deemed to be at nutritional risk following preoperative screening, to either 5 days of preoperative oral immune-enhanced nutrition or an isocaloric isonitrogenous standard oral feed. The primary study outcome was overall complication rate, with a secondary outcome of infection complications, including wound infection, urinary tract infection, intra-abdominal abscess, pneumonia, and sepsis. Results demonstrated no significant differences between the rate of overall complications (p=0.699) or infection complications (p= 0.488); although it was noted that compliance with the oral supplementation regime was low (53% in the immune-nutrition group and 60% in the standard nutrition group), with an actual preoperative intake of allocated supplements falling below manufacturer recommendations in 43% of the included patients. Previous meta-analysis of 21 studies by the same authors (Cerantola et al, 2010) had suggested there was a benefit of immunonutrition on postoperative morbidity, although the authors recognised significant heterogeneity with respect to demographics, nutritional risk definition, operation and nutritional intervention. The overall benefit of targeting nutrition prior to surgery only became overt by pooling these trials. Within paediatrics, similar evidence is lacking.

3.2.4 Cardiac SSI and surveillance at the study hospital

The study hospital was a large, tertiary children's hospital in England. Here, approximately 400 congenital heart operations are performed each year in children from birth to aged 18 years. There is a designated cardiac ward caring for children requiring both medical and surgical treatment of congenital and acquired heart disease, and a 20-bedded regional paediatric intensive care unit providing services to all medical and surgical sub-specialties.

Following departmental concern regarding an increase in wound infection rates after a change in postoperative antibiotic prophylaxis in 2008, the process of auditing cardiac SSI rates began in 2010. The SSI classification methodology adopted for case identification was the CDC criteria in place at the time of the study (Horan et al, 2008), therefore from 2010 onwards all postoperative complications of SSI were prospectively entered into the cardiac surgical departmental database along with demographic, diagnostic and operative characteristics routinely collected, and subsequently reported monthly at the departmental mortality and morbidity review meeting. With reducing hospital acquired infection being regionally agreed as a performance target (CQUIN Payment Framework item), cardiac SSI data was additionally presented at the study hospital's Infection Prevention and Control Committee meeting, chaired by the Director of Infection Prevention and Control (DIPC). Additionally, in 2011 the study hospital agreed reducing HAI would be a key quality and safety indicator for the 2013/2014 Trust quality strategy.

With this increasing awareness, both locally and nationally, on the reduction of SSI as being a priority for patient care, November 2011 saw the introduction of the paediatric cardiac surgical site infection 'care bundle', promoting the standardisation of elements of care for every paediatric cardiac surgical patient, all of the time. Although not part of this research, this process commenced with a review and synthesis of the relevant literature regarding best evidence and practice for reducing SSI, with a view to their potential inclusion, and established the standard of care that all patients entering this study would have been expected to receive. A multi-disciplinary meeting involving relevant stakeholders was held to agree the care bundle. Individual elements which would be applied during the preoperative, intraoperative, and postoperative phases of cardiac surgery were subsequently agreed by consensus (the final bundle can be viewed in Appendix 11).

Nasal carriage of Staphylococcus aureus has consistently been associated with increased rates of health-care associated infection (Huang et al, 2013; Spencer et al, 2012), and has been recognized as a major pathogen in SSI after adult cardiac surgery (Kluytmans et al, 1995). A randomised controlled trial by Bode et al (2010) enrolled 917 patients who were positive for methicillin and mupirocin sensitive Staphylococcus aureus, most of whom (n= 808) underwent

surgery. This trial demonstrated that treatment with intranasal mupirocin with chlorhexidine bathing compared to placebo reduced the relative risk of nosocomial infection to 0.42 (95% CI 0.23 – 0.75). The effect was more pronounced for deep surgical site infections (RR 0.21, 95% CI 0.07 – 0.62). Although similar evidence in paediatric cardiac surgery is lacking, the bundle included the screening and decolonisation of Staphylococcus aureus for all preoperative cases, in addition to the existing hospital-wide admission screening and decolonisation policy for methicillin-resistant Staphylococcus aureus. Any child identified as a carrier would undergo a decolonisation regimen for 5 days immediately prior to their surgical date, using nasal mupirocin and an anti-microbial wash solution. This was the only bundle element which had a strong evidence base in adult surgical populations (Bode et al, 2010).

For the rest of the bundle components (e.g. reducing theatre traffic through minimising door openings, using alcoholic skin preparation solutions) the process-of-care elements included are generally based on good practice rather than high-level evidence (Pasquarella et al, 2012; Scaltriti et al, 2007). As such, they are generic rather than specialty specific and follow the existing NICE (2008) guidance. In the main many epidemiological studies that define the burden of, risk factors for, and outcomes associated with healthcare associated infection are primarily based on adult studies (NCCWCH, 2008) and have been extrapolated to the paediatric population. Hospitalized children will differ in the prevalence and array of comorbid conditions, their exposure to medical devices, and potential carriage of antibiotic resistant organisms (Coffin & Huskins, 2012) but nevertheless, in the absence of paediatric specific data, have spread into paediatric practice as advocated by the Department of Health (2010).

Following implementation of the agreed bundle in 2011, the following November (2012) after a period of 12-months for the bundle elements to be disseminated and embedded into the practice of the wider clinical teams, monitoring of bundle compliance commenced using a monthly point prevalence audit. However, despite the introduction of the bundle rates of SSI did not alter although compliance monitoring of the agreed bundle appeared to be satisfactory (that is, a cumulative annual compliance rate at over 90%). The question was raised as to whether there were other factors influencing SSI risk in this population group, and which could be potentially targeted as an additional SSI prevention strategy. As has been previously identified, the known relationship between poor growth and congenital heart conditions placed poor nutritional status as a plausible explanation for the continued SSI risk in these children, forming the basis of the research question.

3.3 Aim of the study

To investigate preoperative factors including undernutrition as risk factors for a specific infection (SSI) in a specific paediatric surgical population (cardiac surgery).

The objectives of the study were to:

1. estimate the risk of surgical site infection (SSI) infection in different subgroups of a paediatric cardiac surgical population
2. explore nutritional status as an independent risk factor for SSI
3. identify other independent risk factors for SSI.

3.3.1 Methodology

As the objectives of this study were to estimate risk of SSI and to investigate risk factors for SSI, a cohort design was appropriate design was appropriate. Risk is the probability that an outcome will develop in a defined population over a given period of time. In a cohort study, participants are followed up over time and the risk of disease in the whole population and in those exposed to a factor and those not exposed can be estimated. Relative risk provides an estimate of the likelihood of disease developing in the exposed participants as compared to non-exposed participants; in this case the rate of SSI in the undernourished compared to the rate of SSI in those who are not undernourished. If there is no association between exposure and outcome, the relative risk will be one as risk is the same for both exposed and non-exposed participants. If there is an increased risk with exposure it will be >1, and if the risk is reduced in exposed participants it will be < 1. A 95% confidence interval is usually estimated around the relative risk and the width of the confidence interval is an indication of the precision of the relative risk. In lay terms there is a 95% likelihood that the true effect size lies within the interval range.

Usually a cohort study is set up with prospective data collection. The prospective nature of a cohort study is important for demonstrating the temporal nature of the relationship between the risk factor and the outcome; one of the essential criteria for causal inference as outlined in the Bradford Hill's criteria (Hill, 1965). This comparison between exposed and non-exposed participants is the hallmark of the cohort design (Gordis, 2009). However, a retrospective cohort study can be undertaken when the data on exposures and outcome is already available (e.g. from an administrative database) and when it is clear that information on the exposure has been measured or was available before data was collected on the outcome. This is the case for this study.

Many of the features of the database in this study also reduced potential study biases. The robust SSI identification procedure with Consultant validation was embedded within the department for all patients and using a standard definition. Consequently, this eliminated the potential for observer bias as all SSI outcome had been pre-determined prior to study commencement. In addition, this process which was applied to all patients and the short time interval between exposure and outcome, led to no loss to follow up.

One of the disadvantages of a cohort study is that, because exposures are not randomly applied, there may be differences in the characteristics of those who are exposed and those who are not exposed, which are also related to outcome, and a perceived relationship between the exposure of interest and outcome when one does not really exist. These characteristics are called confounders. Potential confounders might be known from other studies on risk factors for SSI or there might be strong indirect evidence. They need to be accounted for in the study, either through restriction (that is limiting the participants according to specific characteristics), matching the two groups on specific characteristics or, more usually, through using multivariate analysis techniques on the data, appropriate to the nature of the data. Multivariate techniques produce an odds ratio, an estimate of the relative risk, for the exposure of interest following adjustment for the other variables. Undertaking this type of analysis provides information not just on whether the exposure of interest is a risk factor, but on whether the other characteristics included in the analysis are also risk factors when all variables are adjusted for in the analysis.

The reliance on a single administrative database in one hospital is that it may limit the generalizability of the study findings if care is different from other settings, but the time required, and costs involved, when compared to setting up a prospective study are substantially reduced. A single site study also means that there is a restriction in the number of operators and patients receive similar pre, intra- and postoperative care reducing the effect of these factors on the relationship between undernutrition and SSI.

3.4 Methods

3.4.1 Study design

A single-site, retrospective cohort study was undertaken to identify whether undernutrition is a risk factor for surgical site infection following paediatric congenital heart surgery. Utilisation of a surgical database maintained by the department of paediatric cardiac surgery enabled data capture on large numbers of patients. This had the advantage of being able to use historical data to identify a defined population for the retrospective two-year study period at the time of surgery. This enabled retrospective data extraction on the prospective data

collection of related surgical outcomes, to an agreed, standard method, for the required duration of follow-up to ascertain whether the outcome of interest had occurred. During the process of retrospective data extraction, the exposure of interest was ascertained using prospectively collected data (that is, body weight and age at surgery).

A retrospective analysis, in addition to the above, had the advantage in that as the existence of a robust SSI identification procedure had been embedded within the department, bias in outcome assessment was minimised, as outcome event data (SSI) had already been determined for all participants at the start of the study. Timing of the study (2013-2014) also permitted a minimum follow-up of one-year post-surgery, allowing for maximum SSI surveillance of one-year for all participants. The cohort design is appealing because there is minimum loss to follow-up (attrition) of the study population and conducting this type of study is particularly suitable when the interval between exposure and disease development is short, and where disease incidence is at low rates.

A cohort study enables a comparison of rate of SSI development between those participants classified as undernourished compared to those who are not. The hypothesis would be that rate of development of infection (incidence) would be higher in the exposed group. Incidence is a measure of risk (Gordis, 2009) and can be defined as the probability of an event, such as disease development, occurring within a specified time. The odds ratio (which approximates the relative risk) provides an estimate of the likelihood of disease developing in the exposed participants as compared to non-exposed participants. If there is no association between exposure and outcome, the odds ratio will be one (OR = 1) as risk is the same for both exposed and non-exposed participants. If there is an increased risk with exposure the odds ratio will be >1, and if the risk is reduced in exposed participants the odds ratio will be < 1. The odds ratio is usually presented with the 95% confidence interval, and if this interval does not contain the value of 1 there is good evidence that the estimated odds ratio is significantly different to 1 at the 5% level of significance.

The advantage of using a single-site was that during the period of study there was consistency in both the consultant and middle-grade surgical workforce. In addition, the standardisation of pre, intra- and postoperative care as part of the adopted care bundle would, it was hypothesised, minimise variance in routine aspects of care, and assist in the identification of independent risk factors for SSI.

3.4.2 Data collection methods

Potential participants were identified using the departmental cardiac surgical patient database as the primary data source. This is a database prospectively maintained by the cardiac surgical

team and used to capture data on all patients undergoing congenital heart surgery. Data collection and data entry were performed by the junior surgical team, with data capture commencing at the time of operation, with diagnostic, operative and co-morbidity data items entered. Procedural and complication data were then entered prospectively throughout the inpatient stay. Late complications occurring after hospital discharge were also captured for purposes of national outcome reporting and quality assurance purposes. At the time of this study, database entries were validated weekly by a member of the consultant surgical team for accuracy and completeness of data.

The process of prospective inpatient SSI surveillance in place at the time of this study (2012-2014), along with all post discharge reviews of wound related complications being carried out by the surgical team, ensured a robust method of data capture. The surgical database served as the primary mechanism for the identification of cardiac SSI data. All SSI cases were reviewed and validated by a consultant cardiac surgeon, prior to reporting and submission of cardiac SSI data to the study centre's trust-wide Infection and Prevention Control Committee.

3.4.3 Setting

The study site was a tertiary paediatric congenital heart surgical centre in England. Following surgery, all patients spend a minimum of one night on the designated paediatric intensive care unit prior to transfer to a dedicated cardiac ward.

3.4.4 Participants

3.4.4.1 Inclusion criteria

All patients less than 18 years of age who underwent palliative or corrective surgery for congenital heart disease, via median sternotomy or posterolateral incisions, between 1st January 2013 and 31st December 2014 were evaluated. These incisions were chosen as they are the main surgical approaches in any operation to correct or palliate congenital heart disease.

Participants were included if during the study period they underwent:

- first operation for congenital heart disease
- staged re-operation for congenital heart disease, where prior surgery occurred more than 12 months previously.

3.4.4.2 Exclusion criteria:

- Re-operation for palliation or correction of congenital heart disease, where prior cardiac surgery has been performed within 12 months, and where the patient is still receiving active SSI surveillance (please see section 3.4.5.4 for justification of exclusion).

- Operations for pectus malformation or other non-congenital heart disease pathology.
- Operations in ventilator dependent neonates requiring surgery for persistent patent ductus arteriosus (PDA) closure, because postoperative recovery does not occur in the study centre.
- Isolated extra-corporeal membrane oxygenation (ECMO) support procedures because this will not require surgical correction/palliation of congenital heart disease.

3.4.5 Exposure and outcome

3.4.5.1 Definition of exposure

The exposure of interest was undernutrition and weight-for-age z-scores (WAZ) were chosen to categorise patients into nutritional class. Weight-for-age reflects body mass relative to chronological age, being influenced by both height-for-age and weight-for-height. Its composite nature makes interpretation complex; for example, weight-for-age fails to distinguish between short children of adequate body weight and tall, thin children. However, in the absence of significant wasting in a community, similar information is provided by weight-for-age and height-for-age, in that both reflect the long-term health and nutritional experience of the individual (de Onis & Blossner, 1997). As operative weight and date of birth were both recorded in the dataset for each participant, WAZ scores could be calculated for each patient utilising CDC Growth Chart Data Tables for *z*-score values available at http://www.cdc.gov/growthcharts/data_tables.htm.

Patients were categorised into three groups – *normal* as defined by a z-score between -2 and +2 standard deviation scores (SDS); *underweight* as less than -2 SDs; and *overweight* as those with z-scores greater than +2 SDs. For the purpose of this retrospective analysis, a WAZ score less than -2 SDs was chosen to define the exposed group, as both weight and age could be prospectively extracted from the surgical database to calculate the WAZ score. Also, a WAZ score less than -2 SDs has been used in the recent published literature with regard to this specialist paediatric surgical subgroup (Eskedel et al, 2008; Mitting et al, 2015; Anderson et al, 2011). This variable was chosen over absolute body weight as the latter is highly correlated with age, which has consistently been shown to be a risk factor for SSI (Allpress et al, 2004; Sarvikivi et al, 2008; Sohn et al, 2010). Additionally, an age-independent weight metric could be used in the model, so that patient age could be added as a separate variable.

3.4.5.2 Definition of outcome

The main outcome was development of surgical site infection (SSI). Definition and categorization of SSI were per CDC criteria (Appendix 9). All cases had been prospectively

identified and verified as an SSI complication within the cardiac surgical database, from which data related to this outcome were extracted.

When patients died within 30 days of operation (or day of non-primary wound closure if sternotomy wound was left open on the day of surgery), or when patients were re-operated on and died within 30 days of their initial surgery (or day of non-primary closure) without an SSI diagnosis, SSI outcome was unknown. Operations on patients in either of these categories were therefore excluded from the analysis. Where patients were re-operated on within 30 days and survived, SSI outcome was calculated from the date of re-operation.

Operations on patients having previous cardiac surgery within the preceding 12 months were excluded from the study. This permitted the application of the 1-year CDC follow-up criteria for the use of 'implants', as the use of non-human material is commonplace in most paediatric cardiac surgical procedures. Applying the exclusion criteria allowed SSI outcome to be attributed only to the operation included in the study dataset, and not from an earlier operation for which the patient may still be under a period of SSI surveillance. This strategy enabled ascertainment that the outcome of interest (SSI) was not present at the start of the study, which is an important quality assessment measure for cohort studies (Wells et al, 2011).

3.4.5.3 Potential predictors of SSI

From the primary data sources, demographic, preoperative and perioperative clinical variables were extracted based on reported univariate and independent risk factors for SSI infection following paediatric cardiac surgery, as identified from prior cohort and case control studies – that is Level III evidence as per the 2009 CEBM classification. These included the following patient variables: age at surgery (Costello et al, 2010; Algra et al, 2012; Murray et al, 2014; Hatachi et al, 2018); non-cardiac comorbidity (Rosanova et al, 2009; Barker et al, 2010; Nelson-McMillan et al, 2016); previous cardiac surgery (Barker et al, 2010) and preoperative length of stay (Sarvikivi et al, 2008). The following operative variables were used: surgical risk (Barker et al, 2010; Algra et al, 2012); use and duration of cardiopulmonary bypass (Barker et al, 2010; Costello et al, 2010; Turcote et al, 2014); use of delayed sternal closure (Johnson et al, 2010; Algra et al, 2012; Murray et al, 2014; Nelson-McMillan et al, 2016) and use of extra-corporeal membrane oxygenation (Barker et al, 2010; Turcote et al, 2014). Weekday of surgery was also extracted as this has previously been found to be associated with increased SSI risk (Holzmann-Pazgal et al, 2008). All these data were available from the prospectively maintained departmental surgical database. Where appropriate, quantitative risk factors, such as preoperative length of stay, were converted from continuous to categorical variables in case the modelled response was non-linear, and to aid interpretation of tabulated results.

In addition, haematological and biological data were extracted for each patient from the hospital information system. Similarly, all blood values extracted from the patient's record were categorised as low, normal or high, in accordance with reference ranges for age as governed by the hospital's laboratory procedure manual. Preoperative serum albumin and ferritin levels were extracted as they have both been implicated as potential indicators of nutritional status and are known to be affected by inflammation and infection (Leite et al, 2005; Thurnham & McCabe, 2012). Preoperative serum haemoglobin was extracted as a potential marker for cyanosis in the absence of preoperative oxygen saturation levels (Rosenthal et al, 1971).

Operation complexity was calculated from the operative procedure performed using the Basic Aristotle Score (BAS) classification system (Lacour-Gayet et al, 2004). This is a consensus procedure-adjusted complexity score, classifying operations per the potential risk of mortality, morbidity and estimated technical difficulty. This was chosen over the Partial Risk Adjustment in Surgery (PRAiS) methodology being used at the time of the study (Pagel et al, 2013) or the Comprehensive Aristotle Score (Lacour-Gayet et al, 2004). This was because the BAS remains independent of patient related complexity, such as patient age, which could then enter the statistical model as a unique variable with minimum risk of collinearity. Hence, the BAS (without modification for patient related factors) would reflect only the technical/procedural aspects of the surgery. When there were multiple procedures per operation, the score was assigned to the most complex procedure.

3.4.5.4 Duration of follow up

Duration of follow-up for all included patients was until completion of the SSI surveillance period - 1-year post-operation when implants were used, 30 days for all others. Implants were defined for this study as permanently implanted surgical material. Passive post hospital discharge surveillance was conducted via cardiology outpatient clinics, with many included patients receiving this primarily at the surgical centre, or otherwise at Consultant Cardiology-led clinics located at the nearest paediatric cardiology centre (30 miles away) or at regional paediatric cardiology clinics. Following cardiac surgery, referral back to the surgical service for any wound-related complication was standard practice. All wound healing complications, including SSI, were routinely entered into the surgical database by the reviewing member of the surgical team, with these entries also being used for departmental SSI audit purposes.

3.4.6 Sample size

The data was extracted between 2015 and 2016 on all patients who were operated on between January 1st 2013 and December 31st 2014 to maximise the number of patients available for the analysis and allowing for at least one year follow up of post-surgery, allowing

for maximum SSI surveillance of one-year for all participants. Data on patients operated before this time was not extracted because of concerns about the quality of the database.

There are few published studies that allow the necessary sample size for a logistic regression analysis to be calculated. Most logistic regression analyses quote Peduzzi et al (1996) to justify the choice of sample size and this article has in excess of 4000 citations. This demonstrates that little is known on this topic. Following the rule of thumb suggested by Peduzzi et al, circa 660 observations with an event rate of 12% would support eight covariates in an adjusted (multivariate) model. We planned not to include more than eight covariates in any adjusted model.

3.4.7 Statistical methods

3.4.7.1 Rate of surgical site infection (SSI)

SSI rates were calculated by dividing the number of SSI by the number of participants and presented per 100 participants. 95% confidence intervals around this estimate were then calculated using Minitab 18 (Minitab Inc, USA).

3.4.7.2 Length of stay

As a non-normally distributed continuous variable, the median and interquartile range was used to summarise length of stay data. Comparison of median values between those with and without the outcome of interest was performed using Mann-Whitney *U* nonparametric test. A p-value less than 0.05 was considered statistically significant. Analysis of length of stay data was undertaken in SPSS version 22

3.4.7.3 Development of the model exploring undernutrition and surgical site infection

The statistical modelling framework used to explore the effect of undernutrition on SSI was logistic regression (Hosmer et al, 2013) since the outcome of interest (occurrence of SSI) was binary. Some patients underwent more than one operation and so, in theory, the data structure could be multi-level with variability at the patient level and variability at the operation within patient level. In this case, account would need to be taken in the modelling of the correlation between multiple operations on the same patient and therefore a multilevel binary logistic regression model would have been appropriate.

It was decided *a priori* that if laboratory data were missing, imputation of missing values would not be undertaken because there was no sound basis for doing this. Consequently, cases with variables with missing data were excluded from the statistical analyses when the numbers of missing values were small, and it was acknowledged that this would reduce sample size by a small amount. If the extent of missing values was deemed large, then the variable was not

included in any analyses. For example, 49% of values for preoperative ferritin were missing, therefore this potential predictor variable was excluded from any analyses. Figure 3.1 shows a summary of the steps in model development. A univariate model is defined as a model with a single predictor and is often called a univariate analysis. It is the simplest method of describing a relationship between a predictor variable and the outcome. It acts as a screening process in order to identify potential predictor variables (or risk factors). However, it does not adjust for the combined effect of other predictor variables which may be impacting on outcome. An adjusted model, therefore, is one which includes several predictor variables, and is often called a multivariate analysis, and regression analysis can predict a dependent variable (outcome) from one or more independent predictor variables (Myles & Gin, 2001).

3.4.7.2 Variable selection strategy

Potential predictor variables were excluded from univariate analysis when rates of incidence were less than 3%, to prevent small numbers of cases becoming highly influential. This excluded two potential patient predictor variables (prematurity and other chromosomal abnormalities apart from Trisomy 21) from univariate analysis. The chosen operative predictor variable 'location of operation' was collapsed and entered modelling as a binary variable – main theatre or temporary theatre – as maintenance work within the operating theatre department necessitated a change of cardiac theatre location for part of the study period. Operations occurring in the Cardiac Catheter Laboratory were excluded due to small numbers (n= 2).

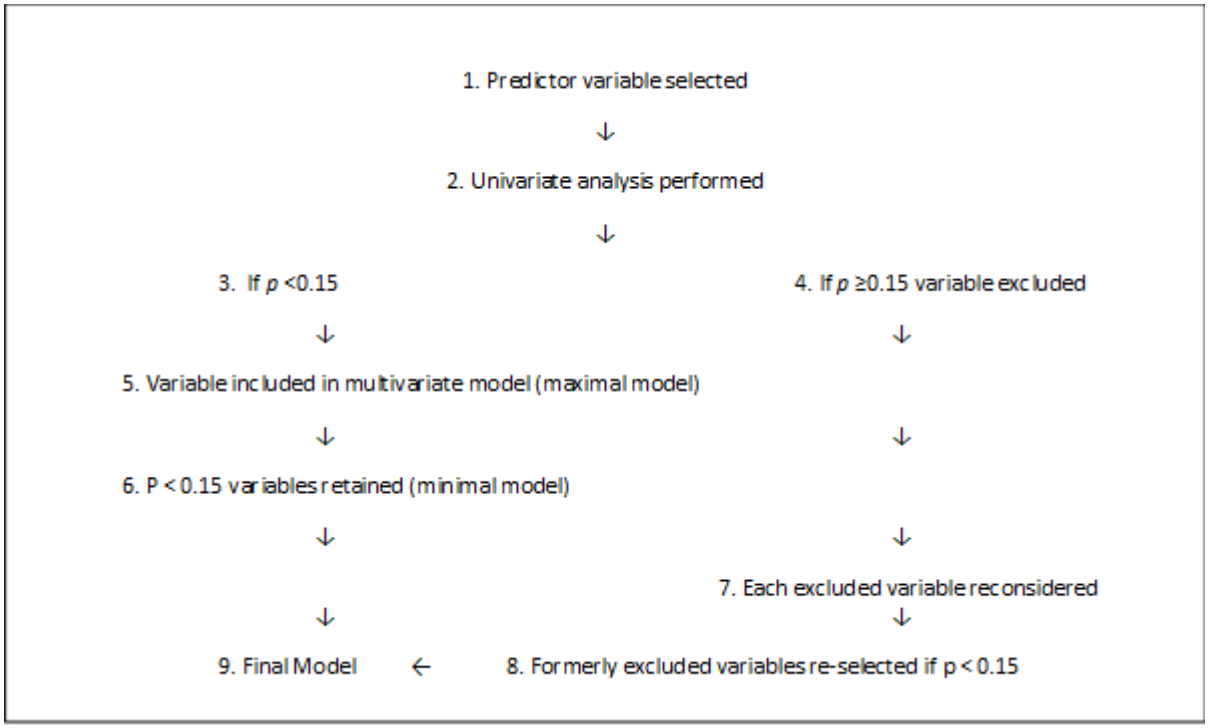
A summary of the variable selection process is provided in Figure 3.1. Univariate logistic regression was used to assess the potential association between each predictor variable and the presence of surgical site infection (step 2). For the next step, potential predictor variables (risk factors) were selected if the *p*-value for Wald's test was less than 0.15 in the univariate analysis (step 3) or excluded if the *p*-value > 0.15 (step 4). This *p*-value criterion of 0.15 was chosen because this was an exploratory study into potential risk factors for SSI. The *p*-value of 0.15 for forward selection of predictors is virtually equivalent to using the Akaike Information Criterion (Akaike, 1974) for forward selection of a single variable, and this threshold *p*-value is in common usage. Selected variables then entered a multivariate logistic regression analysis to identify independent risk factors for SSI using the same *p*-value criterion of 0.15 (step 5). This model was termed the 'maximal model'. If a predictor variable had more than two categories, it was entered in the model if any category showed a *p*-value less than 0.15.

The test *p*-values in the maximal model were scrutinised and potential predictors were removed if the p-value exceeded 0.15 for all categories. All variables achieving a p-value less than 0.15 in the maximal model were retained to form the 'minimal model' (step 6). In the

final stage, all predictor variables that were excluded from the maximal model at step 4 were added individually to the minimal model (step 7). If any of these showed a *p*-value less than 0.15 it was selected for inclusion in the final model (step 8). The final model (step 9) thus contained all the variables in the minimal model plus those variables additionally selected in the final stage.

It is important to determine a variable selection strategy in advance of data analysis to avoid subjective bias in the selection of variables, although some variables (such as age and gender) might be chosen *a priori*.

Figure 3.1: Flow diagram for variable selection



3.4.8.3 Goodness of fit

Model evaluation and goodness of fit included Receiver Operating Characteristics curve and Hosmer-Lemeshow's chi-square test statistic (Hosmer et al, 2013).

Classification tables were used to assess the sensitivity and specificity of the final model in predicting risk of SSI. A receiver operating characteristic (ROC) curve shows sensitivity plotted against 1-specificity for the entire range of possible risk cut points. This measure is now the standard for evaluating a prognostic model's ability to assign, in general, higher probabilities of the outcome to the subgroup who develop the outcome than it does to those who do not (Pepe, 2004). Therefore, the area under the curve (AUC) was used to evaluate the final model's ability to discriminate between those children experiencing SSI and those children that did not.

All regression analyses were performed using IBM SPSS Versions 21 and 22, with Excel used for plotting of the final ROC curve.

3.4.8 Ethical considerations

All research has a responsibility to ensure the rights and general well-being of their participants are maintained, regardless of the nature of the research. Ethical obligations to vulnerable individuals – in the case of this study, minors - necessitate special procedures to protect their interests. However, as this was a retrospective study utilising previously collected data, it did not involve any participant being at risk of potential harm, discrimination, deception or exploitation. Although the primary researcher is a clinician within the cardiac surgical department, due to the use of historical departmental data there was no potential power imbalance or conflict between the two roles. It was agreed that if unforeseen needs arose during the study period which lay outside of the primary researcher's knowledge, skills or expertise, that these would be discussed with the supervisory team.

3.4.8.1 Ethics Approval

NHS Health Research Authority decision tools were completed online with the conclusion that the study was not classified as research that would require NHS ethics approval. This decision was primarily because patients were not to be randomised to different treatment groups; the study protocol did not demand that treatment or care would be changed from accepted standards; and the study findings would not be generalizable to other patient groups. In addition, there would be no collection of additional data that would need specific consent. Consequently, the study was approved and registered as an audit with the hospital's research and development department (Audit registration number 3575), and granted ethics approval by the Business, Science and Health Ethics Committee, University of Central Lancashire (BuSH 201, Appendix 10).

Within the department, a two-stage cardiac surgical consent process was being implemented. Both stages were accompanied by written documentation specific to the child's operation. The first stage, primarily information provision, was usually performed by a member of the junior surgical team. The documentation accompanying this stage included the specific statement:

"Prospective and retrospective anonymized patient data is used for regular internal audits conducted or approved by the cardiac surgical team. The information is also analysed for local, national and international presentation and publication".

This was recognised as being implied consent for this data-based project, with the study lying within the agreed parameters for this form of consent.

3.4.8.2 Confidentiality

Patients were assigned a unique code (Study ID) enabling de-identification of study data, with all subsequent data handling performed using this code. This was a reversible process, so that if required for data verification purposes, individual patient data could be checked.

During active data extraction and the merging of data from hospital information systems and the surgical database, identifiable patient data and their relevant codes were computerised and kept on the Trust's secure network, accessible by password only, with any non-computerised identifiable patient information kept in a locked cabinet at the study hospital. Both were accessible solely by the primary researcher.

3.4.8.3 Data management

Data from the surgical departmental Access database were directly exported into Microsoft Excel, with data items from the hospital information system being entered manually. Due to specifications in place for hospital information systems, processes were deemed to be sufficient to assume extracted data were valid with no requirement to re-validate. The weekly consultant validation of the surgical database ensured operative data and complication data were complete. Data cleaning occurred to identify any demographic (e.g. gender, date of birth) or hospitalisation data (e.g. date of admission, date of discharge) omissions from the surgical database. Where possible, any missing data were retrieved from the hospital information system and entered manually. IBM SPSS versions 21 and 22 were used for subsequent data analysis and statistical modelling.

3.4.6.4 Data Storage

All identifiable patient data were stored electronically on the secure network at the study hospital. Non-identifiable patient data were temporarily stored on the University of Central Lancashire's network for the purposes of data analysis only. Both systems were user-specific to the primary researcher or members of the supervisory team, and individually password protected.

During active data collection, all manual records (data extraction sheets) with identifiable patient information were kept securely in a locked cabinet within a shared locked office on site at the study hospital, in line with existing NHS information governance standards (Mitchell, 2016). At the end of the study, computerised, non-identifiable study data collected as part of the study were stored, with a back-up, on the hospital Trust's secure network drive, with all non-electronic material containing personal data disposed of via the Trust's confidential waste service, as per the Trust's Code of Good Practice for Clinical Audit (2011).

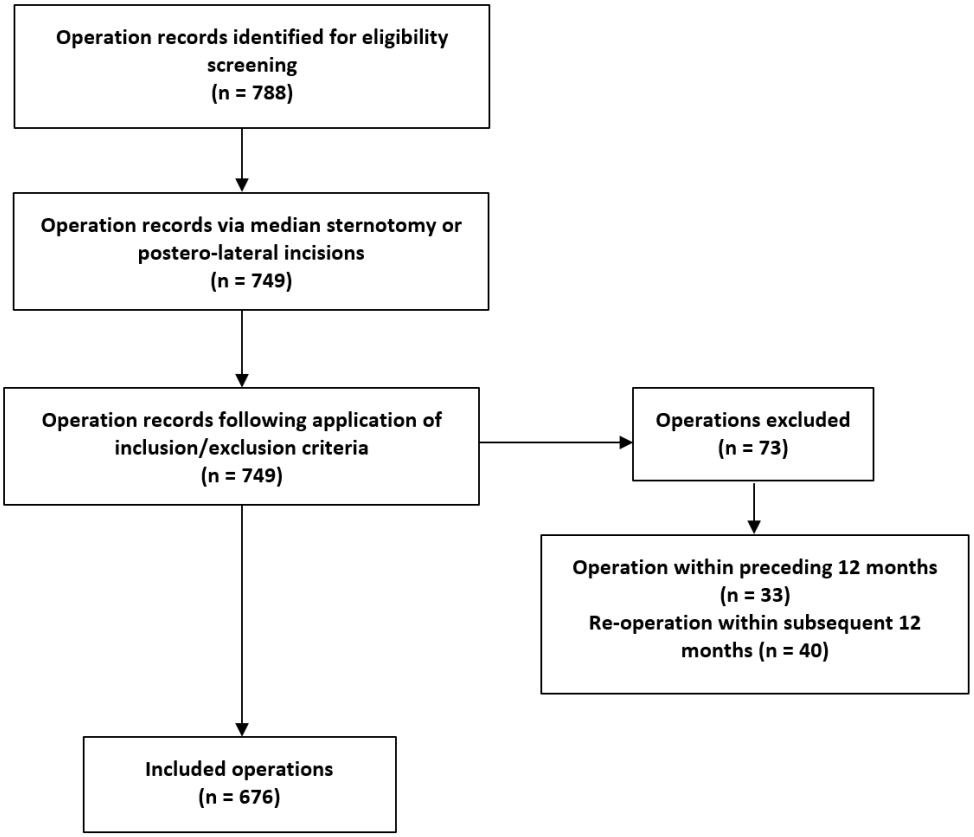
3.5 Results

3.5.1 Results of eligibility screening

A total of 788 operations were performed for palliation or correction of congenital heart disease during the two-year study period (1st January 2013 – 31st December 2014). Of these, 749 operations were performed via median sternotomy or posterior-lateral incisions and progressed to eligibility screening against inclusion and exclusion criteria.

Following screening, a total of 73 operations were excluded – 33 operations were staged procedures with the child's previous surgery taking place within 12 months and prior to study commencement; a further 37 operations were staged reoperations in patients during the study period where previous staged surgery was within 12 months; and 3 were unplanned reoperations within the same hospital admission. Therefore, a total of 676 operations were included. On review of these, all 676 operations were in unique patients who only appeared once within the dataset (Figure 3.2) either for their first cardiac operation or for a planned

Figure 3.2: Flow diagram of included operations



staged reoperation not occurring within 12 months of their first operation. Hence, the inclusion and exclusion criteria for operations effectively reduced the data set to one operation per patient, which considerably simplified the statistical modelling approach and removed the need for multi-level modelling.

3.5.2 Patient and operative characteristics

Patient and operative characteristics can be viewed in Tables 3.1 and 3.2 respectively. In terms of patient characteristics, just over 60% of patients were less than 1 year of age with almost 22% being less than 28 days of age. Approximately 20% of the population had had previous cardiac surgery. In terms of weight-for-age *z*-score categories, 28% of patients were in the underweight category, whereas only 1.8% were in an overweight category. Just over 12% of patients had a genetic anomaly, mainly Trisomy 21 (Down's syndrome) which would be expected in this population group. Overall, preoperative carriage of Staphylococcus aureus was 17.6% in those children who were screened preceding surgery, revealing a screening compliance rate of 93%. A high proportion of patients were identified as having low serum albumin concentrations (23.5%) and low serum ferritin levels (43.6%) before surgery. Patient characteristics can be viewed in Table 3.1.

In terms of operative characteristics, most operations occurred during weekdays with the highest number occurring on a Monday when two cardiac theatres were functioning. The majority of operations were in a moderate risk category and undertaken on cardiopulmonary bypass (85%) with durations less than 3 hours and with a delayed sternal closure rate of 15%. Use of extracorporeal membrane oxygenation (ECMO) was 3%, which is consistent with recently reported rates of ECMO use following paediatric cardiac surgery (Bratton et al 2017). During the two-year study period the Consultant surgical team remained constant, with an equal division of operations performed between them over the two-year period. Operative characteristics can be viewed in Table 3.2.

Table 3.1: Patient Characteristics (N= 676)

		n	%
Gender (male)		393	58.1%
Age category	Neonate	149	22.0%
	Infant	259	38.3%
	Preschool	127	18.8%
	School age	131	19.4%
	Adolescent	10	1.5%
Age (days)	Mean (SD)	902.85 (1456.26)	
	Median (IQR)	193 (45 – 1228)	
Weight (Kg)	Mean (SD)	11.43 (13.80)	
	Median (IQR)	6 (3.8 – 13)	
Weight-for-age *Z*-score (WAZ) category	WAZ < -2	190	28.1%
	WAZ -2 to +2	474	70.1%
	WAZ > +2	12	1.8%
Prematurity (Gestation < 35 weeks)		3	0.4%
Down's Syndrome (Trisomy 21)		61	9.0%
22q11 deletion		14	2.1%
Other chromosomal abnormality		7	1.0%
Preoperative Staphylococcus aureus carriage	Negative	495	73.2%
	Positive	119	17.6%
	Unknown	62	9.2%
Preoperative haemoglobin level	Normal	520	76.9%
	Low	70	10.4%
	High	84	12.4%
	Unknown	2	0.3%
Preoperative ferritin level	Normal	50	14.5%
	Low	295	43.6%
	Unknown	331	49.0%
Preoperative albumin level	Normal	511	75.6%
	Low	159	23.5%
	Unknown	6	0.9%
Preoperative C-reactive protein	Normal	535	79.1%
	High	122	18.0%
	Unknown	19	2.8%

SD= standard deviation; IQR= interquartile range

Table 3.2: Operation Characteristics (N= 676)

		n	Median (IQR)	%
Location of operation (operating room [OR])	Main cardiac 1 (OR 7)	508		75.1
	Main cardiac 2 (OR 6)	93		13.8
	Temporary cardiac 1 (OR 2)	69		10.2
	Temporary cardiac 2 (OR 5)	4		0.6
	Cardiac Catheter (OR 8)	2		0.3
Use of cardiopulmonary bypass (CPB)		571		84.5
Duration of CPB in minutes			96 (61 – 144)	
Use of deep hypothermic circulatory arrest		12		1.8
Cardiac operation number in patient's lifetime	1	544		80.5
	2	71		10.5
	3	39		5.8
	4	19		2.8
	5	3		0.4
Operation risk category n= 674* (Basic Aristotle Score)	0 – 3	68		10.1
	3.1 – 6	169		25.0
	6.1 – 9	342		50.6
	9.1 – 12	72		7
	12.1 – 15	23		3.4
Diagnostic category	1 Two ventricles, no LVOTO	493		72.9
	2 Two ventricles with LVOTO	92		13.6
	3 One ventricle, no LVOTO	48		7.1
	4 One ventricle with LVOTO	43		6.4
Use of ECMO[0]		17		12.5
ECMO days			3 (2 – 6)	
Delayed sternal closure (DSC)		88		13.0
DSC days			2 (1 – 4)	
Theatre Team (classified by attending surgeon)	1	241		35.7
	2	223		33.0
	3	212		31.4
Day of operation	Monday	167		24.7
	Tuesday	131		19.4
	Wednesday	148		21.9
	Thursday	110		16.3
	Friday	106		15.7
	Weekend	14		2.1
Year of surgery	2013	351		51.9
	2014	325		48.1

[0]ECMO= extracorporeal membrane oxygenation; *2 values missing; IQR= interquartile range; CDC= Center for Disease Control, LVOTO = left ventricular outflow tract obstruction

3.5.3 Surgical site infection

3.5.3.1 Risk of surgical site infection

A total of 10 children died without completing the required period of active surgical site infection (SSI) surveillance but without occurrence of SSI. Six of these children died within 30 days of their operation (early death), one child had reoperation, and died within 30 days, and three children were placed on extracorporeal membrane oxygenation (ECMO) via chest cannulation. In situations where primary sternal closure does not occur at the end of surgery, SSI surveillance continues for 30 days from day of delayed sternal closure. The latter three children died during this follow-up period.

As deaths occurring during active SSI surveillance when SSI outcome was unknown were excluded from further analysis, this represented a 1.5% loss in sample size. Of the remaining 666 children, 79 experienced a surgical site infection as per CDC definition, giving an SSI rate of 11.9% (95% CI, 9.5 – 14.6%). As can be seen from Table 3.3, the majority were in the superficial SSI category (83.5% of all SSI), with one quarter of overall SSI complications being found in the neonatal age group which was of both statistical and clinical significance.

Table 3.3: Category of surgical site infection (SSI) as per CDC classification by age category

N= 666		**Age category**					**SSI**		
		Neonate n=145	**Infant n=256**	**Pre-school n=125**	**School age n=130**	**>16yr n=10**	**n**	**%**	**95% CI**
CDC SSI category	**Superficial**	33	18	9	6	0	66	9.9	(7.7 – 12.4)
	% of age group	(22.8%)	(7.1%)	(7%)	(4.6%)				
	Deep	4	2	2	3	0	11	1.7	(0.8 – 2.9)
	% of age group	(2.8%)	(0.8%)	(1.6%)	(2.3%)				
	Organ/Space	0	1	1	0	0	2	0.3	(0.04 – 1.1)
	% of age group		(0.4%)	(0.8%)					
	Total	37	21	12	9	0	79	11.9	(9.5 – 14.6)
	% of age group	(25.6%)	(8.3%)	(9.5%)	(6.9%)				

*****Death/reoperation during 30-day active SSI surveillance =10 (neonates=3; infants = 5; preschool = 1, child = 1)

Table 3.4: SSI incidence by patient and operative characteristics (N=666)

		n	n with SSI*	% SSI
Gender (n= 666)	Male	389	45	11.6
	Female	277	34	12.3
Age (n= 666)	Neonate	145	37	25.6
	Infant	256	21	8.3
	Preschool	125	12	9.5
	School age	130	9	6.9
	Adolescent	10	0	0
Weight for age Z-score (WAZ) category (n= 666)	WAZ < -2	187	13	7
	WAZ -2 to +2	467	65	13.9
	WAZ > +2	12	1	1
Diagnostic category (n = 666)	1 = Two ventricles, no LVOTO	486	50	10.2
	2 =Two ventricles with LVOTO	92	9	9.7
	3 = One ventricle, no LVOTO	47	9	19
	4 = One ventricle with LVOTO	41	11	27
Down's Syndrome (n= 666)	No	607	71	8.7
	Yes	59	8	13.6
Preoperative Staphylococcus aureus carriage (n= 666)	No	486	52	10.7
	Yes	119	18	15.1
	Unknown	61	9	14.8
Preoperative serum albumin (n= 661) Missing = 5	Normal	505	56	11.1
	Low	156	22	14.1
Preoperative serum haemoglobin (n= 664) Missing = 2	Normal	512	53	10.4
	Low	70	14	20.0
	High	82	12	14.6
Preoperative C-reactive protein (n= 657) Missing = 9	Normal	535	60	11.2
	High	122	16	13.1
Operation complexity (n= 666) (0 = low complexity; 5 = highly complex)	0 – 3	67	5	7.5
	3.1 – 6	167	12	7.2
	6.1 – 9	338	44	13.0
	9.1 – 12	70	12	17.1
	12.1 – 15	22	6	27.3
Use of cardiopulmonary bypass (n= 666)	No	102	12	11.8
	Yes	564	67	11.9
Theatre team (n= 666)	1	236	32	13.6
	2	220	31	14.1
	3	210	16	7.6
Previous cardiac operation (n= 666)	0	536	64	11.4
	1	70	7	10.0
	2	39	4	10.3
	3 or more	21	4	19.0

3.5.3.2 Length of stay and SSI

The effect of SSI outcome on duration of preoperative, intensive care and postoperative length of stay was explored. A pragmatic decision was made to dichotomize SSI category into superficial SSI and other SSI based on the implications of clinical management following diagnosis; namely superficial SSI can usually be managed on an outpatient basis without prolonging initial hospital stay or requiring readmission, whereas other categories of SSI will invariably require inpatient treatment and further surgical management. In addition, incidence of mediastinitis and endocarditis after PCS is known to be low - reported as 0.09% for mediastinitis and 0.016% for endocarditis by Kansey et al (2015) but associated with a significant mortality of 16.7% for those with mediastinitis (i.e. 1 in 6 patients) and the one case with endocarditis resulting in death.

As can be seen from the results presented in Table 3.5, irrespective of SSI diagnosis neonates were the group who experienced longer hospital stays than any other age category. When considering the impact of SSI diagnosis on median length of stay, there were no significant differences found in preoperative length of stay between those with or without SSI across all age categories. In terms of ICU length of stay, again durations were similar between those with or without SSI across all age categories. In terms of postoperative length of stay, however, only neonatal median length of stay was statistically significant between those neonates with and without SSI (Independent median test, asymptomatic significance $p = 0.04$).

There were observable differences between durations of length of stay between superficial and other types of SSI in the majority of age categories, but median durations of stay were only of statistical significance for overall postoperative length of stay in neonates ($p = 0.038$) and children 1 -4 yr ($p = 0.49$). However, the absence of statistical significance should not underestimate the clinical significance of the increasing length of stay experienced by children with deep-seated SSI.

Table 3.5: Length of stay by age category and surgical site infection complication

		Age category				
		Neonate n=145	**Infant n=256**	**Preschool n=125**	**School age n=130**	**Adolescent n=10**
Preoperative length of stay (median/IQR) in days	**Cohort N= 666**	4 (2 – 8)	1 (1 – 4)	1 (0 – 1)	1 (0 – 1)	
	No SSI N= 587	4.5 (1 - 8)	1 (0 – 3)	1 (0 – 1)	1 (0 – 1)	1 (0 – 1)
	SSI= 79	4 (2 – 10)	1 (1 – 10)	1 (0 – 1)	0 (0 -1)	
	Superficial SSI N= 66	5 (2 – 10)	1 (0 – 5)	1 (0 – 2)	1 (0 – 1)	
	Other SSI N= 13	2.5 (2 – 11)	11 (9 – 14)	0 (0 – 1)	0 (0 – 1)	
Intensive care length of stay (median/IQR) in days	**Cohort N= 666**	5.5 (3 – 10)	5 (1 – 5)	1 (1 – 2)	1 (1 – 2)	
	No SSI N= 587	5 (3 – 10.75)	2 (1 – 5)	1 (1 – 2)	1 (1 -2)	1 (1 – 3)
	SSI N= 79	6 (4 – 10)	3 (1 – 6)	1 (1 – 2.5)	1 (1 – 1)	
	Superficial SSI N= 66	6 (4 – 10)	2 (1 – 4)	1 (1 – 2)	1 (1 – 3)	
	Other SSI N=13	7.5 (5 – 18)	38 (31 – 62)	1 (1 – 1)	1 (1 – 1)	
Postoperative length of stay (median/IQR) in days	**Cohort N= 666**	13 (8 – 26)	6 (5 – 13)	5 (4 – 9)	5 (4 – 9)	
	No SSI N= 587	11 (6 - 25)	6 (5 - 11)	5 (4-7)	5 (4 - 8.5)	7 (5 - 9)
	SSI N= 79	15 (12 – 28)[$]	8 (5 – 19)	10 (4 – 21) [$]	7 (4 – 31)	
	Superficial SSI N= 66	14 (10.5 - 23)	6.5 (5 - 11)	7 (4 – 13.5)	7 (4 - 20)	
	Other SSI N= 13	37 (24 - 45)	96 (68 - 114)	25 (19.5 – 27)	19 (11 - 34)	

[$] *p*-value <0.05

3.5.4 Case and variable selection for risk factors of SSI

Of the potential patient related and operation related risk factors (Tables 3.1 and 3.2), prematurity, chromosomal abnormality and use of intra-operative deep hypothermic circulatory arrest were excluded from modelling due to a rate below 3%. As there were a low number of adolescent patients (1.5%) with no incidence of SSI, the operations on these 10 patients were also excluded from further statistical modelling. Serum ferritin was also excluded due to the extent of unknown values (49%) since its inclusion would have greatly reduced the power of the model to identify other potential risk factors for SSI. Operations performed on Saturday and Sunday were combined for the purposes of the analysis as 'weekend', with the low numbers (2.1%) reflecting the unplanned/emergency nature of these cases which occurred outside of scheduled operating days.

Univariate analysis was performed using clinical variables of gender (reference category = male), age (reference category = neonate), WAZ-score classification (reference category = normal), preoperative Staphylococcal aureus status (reference category = no carriage), preoperative serum haemoglobin (reference category = normal), and preoperative length of stay (reference category = 0); and on operative predictor variables of location of operation (reference category = main cardiac theatre); complexity of surgery (reference category = 0 – 3), theatre team (led by attending surgeon)(reference category = Surgeon 1) , weekday of operation (reference category = Monday); and the use of cardiopulmonary bypass (reference category = no), delayed sternal closure (reference category = no) or postoperative extracorporeal membrane oxygenation (ECMO) support (reference category = no). Values were missing for the clinical predictor variables serum albumin and C-reactive protein; and for the operative predictor variable of surgical complexity, therefore univariate analyses only included known values accounting for the variability in the analysis sample size. As missing values for most variables were low in numbers and accounted for a reduction in sample size entering model development of between 0.3 – 1.3% (n= 2 to n= 9) of the total population this was not deemed important. Results for univariate regression analyses are shown in Table 3.6.

Following univariate analysis, eight variables were found to be associated with SSI at the chosen *p*-value of <0.15. There was a similar number of patient-related risk factors (age, WAZ category, preoperative haemoglobin level and preoperative length of stay) and operation related risk factors (surgical team, surgical risk, use of delayed sternal closure and ECMO). At this point, without adjusting for other factors or each other, seven of the eight variables possessed at least one category that had a statistically significant association with SSI. Of clinical interest, apart from the two variables of preoperative haemoglobin level and the operative team, all remaining variables have been previously reported in the literature as risk

Table 3.6: Results of univariate analyses for surgical site infection (N= 666)

Variables		n	Univariate analysis Odds ratio	*p* value
Gender (n = 666)	Female	277	0.94 (0.58 – 1.50)	0.781
Age (n= 666)	Neonate	145	1	
	Infant	255	0.26 (0.15 – 0.47)	<0.001
	Preschool	126	0.31 (0.15 – 0.62)	0.001
	School age	130	0.22 (0.10 – 0.47)	<0.001
	Adolescent	10	NE[1]	
Weight for age Z-score (WAZ) category (n= 666)	WAZ < -2	187	0.46 (0.25 – 0.86)	0.015
	WAZ -2 to +2	467	1	
	WAZ > +2	12	0.56 (0.07 – 4.43)	0.584
Down's Syndrome (n= 666)	Yes	59	1.18 (0.54 – 2.60)	0.673
Preoperative Staphylococcus aureus carriage (n= 666)	No	486	1	1.000
	Yes	119	1.49 (0.83 – 2.65)	0.178
	Unknown	61	1.45 (0.67 – 3.10)	0.345
Preoperative serum albumin (n= 661)	Low	156	1.32 (0.78 – 2.24)	0.309
Preoperative serum haemoglobin (n= 664)	Low	70	2.17 (1.13 – 4.15)	0.020
	Normal	512	1	
	High	82	1.46 (0.76 – 2.92)	0.251
Preoperative C-reactive protein (n= 657)	High	122	1.20 (0.66 – 2.16)	0.554
Theatre location of operation (n= 665)	Temporary	79	1.37 (0.69 – 2.72)	0.374
Preoperative length of stay in days (n= 666)	0	181	1	
	1	263	0.75 (0.38 – 1.49)	0.412
	2 – 3	63	1.82 (0.79 – 4.22)	0.162
	4 – 7	73	2.50 (1.17 – 5.31)	0.018
	8 or more	86	2.55 (1.24 – 5.25)	0.011
Theatre team (n= 666)	1	236	1	
	2	220	1.05 (0.61 – 1.78)	0.869
	3	210	0.53 (0.28 – 0.99)	0.046
Previous cardiac operation (n= 666)	0	536	1	
	1	70	0.82 (0.36 – 1.87)	0.635
	2	39	0.84 (0.29 – 2.46)	0.753
	3 or more	21	1.74 (0.57 – 5.32)	0.335
Year of surgery (n= 666)	2014	321	0.79 (0.49 – 1.27)	0.329

Variables		n	Univariate analysis Odds ratio	*p* value
Weekday of operation (n= 666)	Monday	164	1	
	Tuesday	131	0.85 (0.38 – 1.90)	0.688
	Wednesday	145	1.40 (0.69 – 2.83)	0.356
	Thursday	109	1.48 (0.70 – 3.13)	0.309
	Friday	103	1.58 (0.74 – 3.35)	0.235
	Weekend	14	2.52 (0.64 – 10.0)	0.188
Operation complexity Score (n= 664)	0 – 3	67	1	
	3.1 – 6	167	0.96 (0.33 – 2.84)	0.941
	6.1 – 9	338	1.86 (0.71 – 4.87)	0.209
	9.1 – 12	70	2.57 (0.85 – 7.73)	0.094
	12.1 – 15	22	4.65 (1.26 – 17.2)	0.021
Use of bypass (n= 666)	Yes	564	1.01 (0.53 - 1.95)	0.974
Delayed sternal closure (n= 666)	Yes	84	2.77 (1.57 - 4.90)	<0.001
Use of ECMO^{0} (n= 666)	Yes	10	3.27 (0.83 - 12.92)	0.091

*SSI = surgical site infection; ECMO^{0}= Extra-corporeal membrane oxygenation; [1]NE Not estimable as no adolescent had SSI

factors for SSI (see section 3.5.5.3). These eight variables then progressed to multivariate analysis to identify independent risk factors for SSI.

3.5.5 Results following model development

3.5.5.1 Results of included model predictor variables

Following univariate analyses, the patient predictor variables of Staphylococcal aureus carriage, serum albumin and C-reactive protein, and operative characteristics of cardiopulmonary bypass use and weekday of operation were excluded from the multivariate model due to *p* values greater than 0.15. Multivariate logistic regression analysis was therefore performed with the remaining eight risk factors of age, WAZ category, preoperative haemoglobin, theatre team, operation complexity, delayed sternal closure, use of ECMO and preoperative length of stay, and can be viewed in Appendix 12a: Maximal model.

At this stage, only four predictor variables of age, WAZ category, preoperative serum haemoglobin and surgical team achieved a *p* value below 0.15 and entered the minimal model, which can be viewed in Appendix 12b. This model included 654 cases (96.7%) of the total study population.

3.5.5.2 Results of model checking procedures

Each predictor variable previously excluded from the maximal model was then re-entered into the minimal model. Following individual re-introduction, Staphylococcus aureus carrier status

and previous operation had *p*-values below the criterion of 0.15 and were therefore included in the final model. The predictor variables included in the final model, therefore, were the three patient predictor variables identified in the minimal model, that is, age, WAZ category and preoperative serum haemoglobin, one operative predictor variable of the surgical team; in addition to the two variables identified during model checking procedures which were preoperative Staphylococcus aureus carriage and previous cardiac operation within the patient's lifetime.

3.5.5.3 Results of the final model

The results of the final model are shown in Table 3.7. A total of 654 participants were included in this model. Age was an independent predictor of SSI outcome, with all other age groups having considerably lower odds ratios than the neonatal reference category. This reflects the fact that 22% of the surgical population were neonates in this study (144/654), but neonates accounted for 47% of all SSI outcome (37/79).

Having three or more operations via the same incisional site during a patient's lifetime increased the odds of SSI almost fivefold (OR 4.9, 95% CI 1.2 – 20.5). However, due to the low frequency, with only nineteen of the 654 patients undergoing three or more operations, the degree of imprecision is reflected in the wide confidence interval seen in the final model for this variable.

Although testing positive for Staphylococcus aureus prior to surgery did not quite reach statistical significance at the 5% level, the estimated odds ratio was almost double that of not testing positive although the confidence interval just included 1 (OR 1.8, 95% CI 0.98 – 3.4) which has clinical significance in terms of potential risk reduction.

Of the remaining variables in the final model, low WAZ score category and one of the three surgical teams appeared to have some association with a reduction in odds ratio for SSI, but both with confidence intervals including 1.

Preoperative haemoglobin, having persisted through model development achieving significant *p* values at the 0.15 level, at the model checking stage with the re-inclusion of previous cardiac operation was not found to be an independent predictor of SSI. This is postulated to be due to the potential correlation between these two co-variates, as there is likely association between overall number of surgeries in a lifetime and polycythaemia due to cyanosis. This will be addressed further in the discussion. However, undernutrition, as measured by WAZ score less than 2, was not shown to be an independent risk factor for SSI; in fact, the model suggests that being in the underweight WAZ category reduced the risk of SSI since the odds ratio is less than 1 for the underweight group when all age groups are taken together. These results were

Table 3.7 Final model after model checking procedures (N= 654)

Variables in the equation			Multivariate analysis	
		n	Odds ratio	*p* value
Age	Neonate	144		
	Infant	254	0.27 (0.14- 0.52)	<0.001
	Preschool	126	0.20 (0.08 - 0.49)	0.001
	School age	130	0.10 (0.03 - 0.30)	<0.001
Weight for age *z*-score (WAZ) category	WAZ < -2	184	0.56 (0.29 - 1.20)	0.091
	WAZ -2 to +2	460		
	WAZ > +2	10	1.20 (0.11 - 12.75)	0.882
Preoperative serum haemoglobin level	Normal	503		
	Low	69	1.08 (0.52 -2.27)	0.833
	High	82	1.73 (0.76 - 3.93)	0.188
Preoperative Staphylococcus aureus carriage	No	479		
	Yes	115	1.83 (0.98 -3.41)	0.056
	Unknown	60	1.32 (0.58 -3.01)	0.507
Previous cardiac operation	None	529		
	1	68	1.64 (0.54 - 5.02)	0.385
	2	38	2.18 (0.55 - 8.69)	0.270
	3 or more	19	4.93 (1.19 - 20.49)	0.028
Theatre team	1	235		
	2	215	1.22 (0.69 -2.14)	0.495
	3	204	0.56 (0.29 -1.08)	0.084

unexpected and consequently raised a new question of interest regarding the potential relationship between age category and weight category with SSI. Was this apparent risk reduction consistent across all age groups, or did it only apply to some of them?

This was felt to be a pertinent question requiring further exploration at this stage, with the intent to delineate this tripartite relationship further. Results from the analysis up to this point were unable to determine the effect of WAZ within the individual age categories, but were portraying an all category effect. This further exploration began first with looking at the

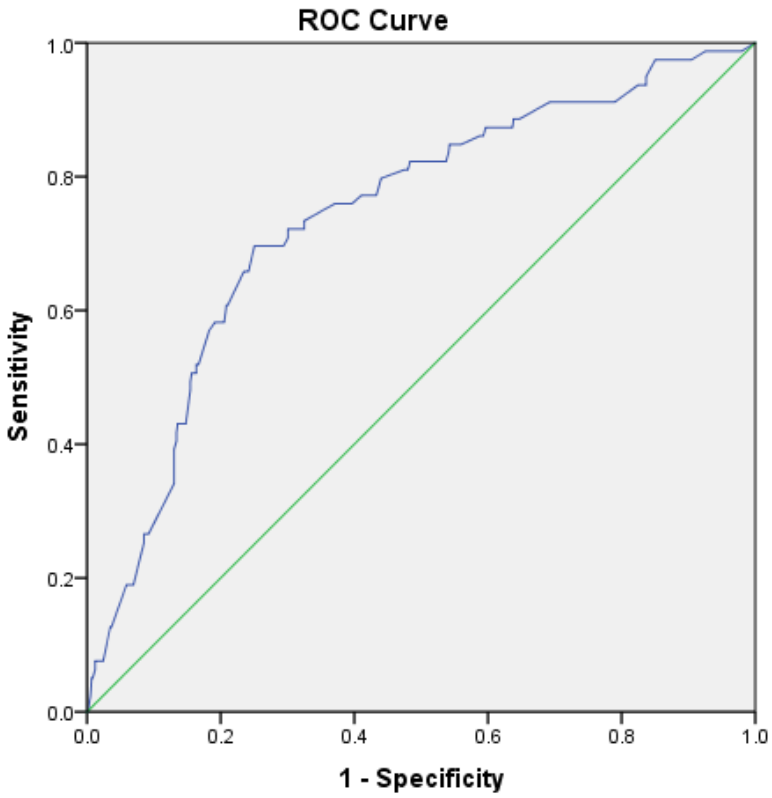
distribution of SSI within the separate age and weight categories, followed by a subsequent reanalysis on the data and the fitting of an interaction term between age group and WAZ group in the model. This will be discussed further in section 3.5.3.4.

3.5.6 Goodness of fit

The area under the Receiver Operating Curve for the final model in Figure 3.4 was 0.74 (95% CI, 0.68 to 0.80), achieving model discrimination at the lower end of acceptable (Hosmer et al, 2013). The Hosmer Lemeshow Chi-square statistic was used to assess the difference between the observed and expected number of SSI. This equaled 2.943 with 8 degrees of freedom, and a *p*-value of 0.938 which indicates adequate fit, as the difference between observed and expected events was small.

The final model, following the variable selection strategy, contained pre-op serum haemoglobin with a *p*-value (for high haemoglobin) of 0.18. However, excluding haemoglobin from the final model led to a reduction in the area under the ROC, therefore confirming the need to retain this variable in the final model.

Figure 3.3 Receiver Operating Curve for the final model



Area Under the Curve = 0.74 (95% CI 0.68 – 0.80)
Hosmer Lemeshow χ^2 = 2.943 (df 8, p=0.938)
Cox & Snell R square = 0.077, Nagelkerke R Square = 0.147

As can be seen from the R Square value, including the patient and operative variables in the model only results in a Nagelkerke R^2 value of 15%, which means as a predictive model it performs poorly at predicting SSI outcome.

3.5.7 Results following further analysis of age and weight-for-age z-scores

In the final model, the variable age had four categories (when adolescents were excluded), and the variable WAZ had three; therefore, the WAZ odds ratio in the final model applied to all four age categories. As the results from the final model were unexpected in that they suggested SSI risk was reduced with having a lower WAZ score, the reasons for this apparent lower risk trend needed to be explored further in order to identify whether it was real, or in fact was a statistical fluctuation and no relationship existed. If this relationship was found not to be a result of collinearity, where due to such a strong relationship existing between two variables of age and WAZ score, then an interaction must be present. If this was the case, it raised the question of whether this effect was consistent across all age groups, or alternatively, was this pattern only present in the neonatal age category where it could be postulated WAZ is more reflective of intrauterine growth and development, rather than nutritional status *per se?*

Consequently, a subsidiary analysis was performed. Firstly, the SSI rate in each combination of age and WAZ category was explored, followed by the development of an additional post-hoc interaction model to explore this relationship more formally. An interaction occurs when the joint effect of two categorical variables cannot be predicted from knowing the individual effects of each. For example, if neonates have half the odds of an outcome of infants, and underweight patients have half the odds of normal weight patients, then underweight neonates might be expected to have a quarter of the odds (half times a half) of normal weight infants. If this expectation is not met, then an interaction is present and the effect of being an underweight neonate is not determined from the overall effect of being a neonate and the overall effect of being underweight.

The distribution of SSI across the age and WAZ categories for the children entering the stages of multivariate analysis are presented in Table 3.8. As can be seen from this table, only 12.4% of neonates are in the <-2SD category, being categorized as underweight. The rate of neonatal SSI in the normal/overweight category (27%), however, was one and a half times that in the underweight category (17%).

In relation to the infants, the WAZ pattern was different to that which was observed in the neonates. Almost half of this age group (46%) were in the underweight WAZ category, with no infant being in an overweight category. With respect to SSI, however, the pattern was similar

to neonates with a reduced SSI event rate occurring in the underweight WAZ category (5% versus 10.9%).

The same pattern was observed again in the preschool age category as for the infants, the underweight WAZ percentage was slightly lower, but the same pattern of SSI is seen with lower rates in this category (6.1% versus 10.9%).

It was only in school-age children that the pattern changes for both WAZ and SSI distribution. Few school-age children were in an underweight WAZ category, whereas the highest overweight WAZ incidence occurred in this age group. SSI incidence was similar in both underweight and overweight categories at 12.5%, whereas the incidence was half this in the normal WAZ category at 5.7%. However, overall SSI incidence within this age category is low, with only 9 school age children out of 130 experiencing SSI (7%) so the significance of these results needs to be interpreted with caution.

Table 3.8 Exploratory analysis of interaction between age and WAZ category (n= 656)

	WAZ category		
Age category	**Less than -2SDS**	**More than -2SDS**	**Total**
Neonates without SSI	15	93	108
Neonates with SSI	3 (17%) 8% of age group with SSI	34 (27%)	37
Infants without SSI	112	122	234
Infants with SSI	6 (5%) 29% of age group with SSI	15 (10.9%)	21
Preschool child without SSI	31	83	114
Preschool child with SSI	2 (6%) 12% of age group with SSI	10 (12%)	12
School age child without SSI	14	107	121
School age child with SSI	2 (16.5%) 22% of age group with SSI	7 (6%)	9
Total	185	471	656

The formal subsidiary analysis undertaken to further explore the result (that being in an underweight WAZ category appeared to reduce rather than increase SSI risk) was a statistical analysis which included the interaction between age and WAZ category in predicting the incidence of SSI.

As there were too few patients in the final model categorised as WAZ > +2 SDS (n= 10) the interaction model contained only two WAZ categories – underweight, and combined normal with overweight - with the age variable remaining at four categories. As only two neonates had been observed in the overweight WAZ category combining the normal and overweight categories would be of little consequence to this age group, which was of particular interest because they demonstrated the highest SSI incidence.

The model in Table 3.9 shows the estimated effect of age and weight status after adjusting for pre-operative serum haemoglobin, pre-op Staphylococcus aureus carriage, previous cardiac operation and theatre team. It shows the overall effect of the WAZ status category within each separate age category. It demonstrates that neonates have a significantly higher risk of SSI than any other of the other age categories overall. Also, within the age categories of neonate to infant, being underweight appears to be associated with a reduced risk of SSI. There are too few underweight preschool and school age children to tell whether the association is present in these age categories since the confidence intervals are wide.

The results also suggest that this may be the opposite for underweight school aged children, where it appears the risk of SSI was higher than when in a normal/high WAZ category. However, it must be noted that the confidence intervals are wide, which indicates the imprecision of these findings therefore caution should be exercised in the interpretation and relevance of these results as findings are also consistent with no relationship. It must also be recognized that in this last age category, SSI incidence in both underweight and overweight categories was similar, therefore the result of combining normal WAZ with overweight WAZ will have lessened the strength of this relationship. It is therefore likely that the true odds ratio of SSI when being underweight is compared to being of normal weight would be higher. The pattern observed in the school age child, however, reflects the evidence for adult surgical populations where being either underweight or overweight reportedly increases overall SSI risk.

Fitting an interaction term between age and WAZ-score category in this way also provided a mechanism for dealing with any potential collinearity that might exist between the variables of age and weight-for-age, as it assists in separating the effect of one on the other by allowing analysis within the age group category. As previously mentioned in the methodology, it is

Table 3.9 Interaction model for age and weight adjusting for other variables

Variables in the equation		n	Multivariate analysis Odds ratio (95% CI)	*p*-value
Age and Age specific Weight for age Z-score (WAZ) category	**Neonate**	**144**	**1**	
	WAZ ≥ -2	126	1	
	WAZ < -2	18	0.43 (0.11 – 1.62)	0.212
	Infant	**254**	**0.27 (0.13 – 0.57)**	**0.001**
	WAZ ≥ -2	137	1	
	WAZ < -2	117	0.47 (0.17 – 1.27)	0.136
	Preschool	**126**	**0.19 (0.07 – 0.50)**	**0.001**
	WAZ ≥ -2	93	1	
	WAZ < -2	33	0.53 (0.11 – 2.67)	0.440
	School age	**130**	**0.08 (0.02 – 0.25)**	**<0.001**
	WAZ ≥ -2	114	1	
	WAZ < -2	16	2.87 (0.50 – 16.37)	0.235
Preoperative serum haemoglobin	Low	69	1.08 (0.51 – 2.26)	0.848
	Normal	503	1	
	High	82	1.72 (0.76 – 3.89)	0.196
Preoperative Staphylococcus aureus carriage	No	479	1	
	Yes	115	1.88 (1.01 – 3.52)	0.048
	Unknown	60	1.35 (0.60 – 3.07)	0.481
Previous cardiac operation	None	529	1	
	1	68	1.78 (0.57 – 5.49)	0.319
	2	38	2.06 (0.52 – 8.18)	0.302
	3 or more	19	5.41 (1.30 – 22.56)	0.020
Theatre team	1	235	1	
	2	215	1.23 (0.67 – 2.18)	0.469
	3	204	0.55 (0.28 – 1.08)	0.082

For the variable Age and Age specific WAZ category OR values in bold indicate the OR of all age categories to the neonatal reference category. Non-bold OR's are the within age comparison between underweight vs reference category of normal weight.

known that age and weight are highly correlated, therefore total body weight could not be used as a variable for this study. Although the study design in using WAZ was to try and control for any correlation, the addition of the interaction term also provides a mechanism for controlling this.

Fitting the interaction did not dramatically alter the results of the final model but did strengthen the evidence for preoperative Staphylococcus aureus carriage being an independent risk factor for SSI, changing what was initially a borderline insignificant result into one of borderline significance (OR 1.88, 95% CI 1.006 – 3.519). It did confirm, however, that neonates have a higher SSI rate irrespective of whether they are underweight or of normal weight, and that a synergistic interaction appears to be evident within the data.

In summary, a different relationship was observed between WAZ and SSI in the different age groups, with a higher risk for SSI in the school age child at both extremes of WAZ, compared with the lower risk observed in the infant and child age group which consistently demonstrated the possibility of a protective effect in being underweight. However, results would also be consistent with no relationship given the confidence intervals around the calculated odds ratio.

3.5.8 Overall summary of mathematical modelling

A total of 656 children were included in the analysis. Following adjustment for both patient and operative variables, logistic regression analyses identified three independent risk factors for SSI. As can be seen from Table 3.9, age less than 28 days was a highly significant predictor for SSI ($p < 0.001$), demonstrating an increased neonatal risk compared to children in all other age categories. Even for neonates who were not underweight the risk was 3.6 times (1: 0.27) the risk for that of infants to as great as 13 times (1: 0.08) when compared to the risk for school aged children. Preoperative carrier status of Staphylococcus aureus demonstrated 1.9 times the risk of SSI (95% CI, 1.01 – 3.52; $p= 0.048$) and undergoing a third or more cardiac operation gave an odds ratio for SSI of 5 (95% CI, 1.30 – 22.60; $p= 0.02$).

3.6 Discussion

The objectives of this study were to estimate the overall risk of SSI within different patient sub-groups, and to explore nutritional status as an independent risk factor for SSI when controlling for other patient and operative characteristics. The main findings will now be discussed within the sub-headings generated from the results of the study.

3.6.1 Rate of surgical site infection

The reported rate of SSI in this cohort study was 11.9% (n= 79), slightly in excess of the highest previously reported rate of 10.9% by Izquierdo-Blasco et al (2015) during their pre-intervention study period, but which is not a statistically significant difference (95% CI, 9.5% - 14.6%). However, reasons for an increased rate when compared to the 3 – 8% previously reported in the literature will be discussed below.

As this study's methodology excluded children having surgery within the preceding 12-months a reduction in the denominator would have occurred which influenced SSI rates. Previously published studies which report SSI use an operation-level rather than patient-level analysis which is in accordance with most SSI surveillance methodology (PHE, 2013), reporting SSI rate per 100 operations which takes account of the fact that the same patient can develop more than one SSI related to the same procedure. The level at which the analysis is undertaken is

important, as this study reported the number of patients experiencing SSI rather than the number of procedures resulting in SSI, and using this method resulted in a rate 2% higher than was identified during unit SSI surveillance for the same time period using the latter definition. In addition, excluded reoperations due to the strict eligibility criteria are likely to be children on a palliative surgical pathway, where staged reoperation usually takes place during late infancy and would therefore be associated with a lower SSI risk. Finally, excluding deaths when SSI outcome was unknown would increase the reported SSI rate than would have been observed had those deaths been included as they are in any operation level analysis. However, as the purpose of the study was to investigate patient-related factors for SSI which might be amenable to modification, rather than operation-related factors which invariably are not, the methodological decisions were felt to be appropriate. Additionally, it was patient outcome (rather than surgical outcome) that was the primary driver for undertaking the study. Any wound-related complication irrespective of an SSI diagnosis will have implications for the child and family, and if it prolongs the period of hospitalization can be viewed as a surrogate measure of quality.

It is well accepted that neonates are relatively more susceptible to infection than older children and adults (Allpress et al, 2004), consistently being reported to be at higher risk of postoperative complications including SSI (Agus et al, 2014; Algra et al, 2012, Padley et al, 2011; Levy et al, 2003). This has been further supported by this study's findings where neonates accounted for 22% of the study population, and experienced 25% of SSI complications. Consequently, studies which exclude neonates (Stey et al, 2014) or have smaller neonatal cardiac surgical programmes are likely to have lower SSI incidence. Trying to extrapolate neonatal outcome data from previously published studies is challenging as SSI incidence is often reported in age categories which include but are not exclusively neonates (Costello et al, 2010; Vivanco-Munoz et al, 2010; Algra et al, 2012; Turcote et al, 2016; Sochet et al, 2017).

The organ/space SSI rate of 0.3% reported in this study is favourable compared to previously published data of 1.2% (Barker et al, 2010). It has been identified that criteria for deep SSI is limited following paediatric cardiac surgery due to the lack of deep soft tissue between the skin and the sternum, therefore, this has led to some studies reporting only superficial SSI and organ/space SSI (Adler et al, 2012; Mangukia et al, 2014), or alternatively only reporting mediastinitis as one type of organ/space infection (Kagan et al, 2007). This heterogeneity in SSI reporting methods makes direct comparison with other cardiac units challenging. However, in terms of outcome, non-superficial categories of SSI appear to have greater consequence on length of stay, as can be seen in Table 3.5 which demonstrates increases are associated with

deeper categories of SSI, whereas lengths of stay with superficial infection appear similar to those without SSI. This is likely explained by the fact that treatment of superficial SSI will not require prolonged hospitalization or, as the majority of superficial SSI is known to present 7 – 14 days after surgery (PHE, 2013) may reflect a post-discharge presentation.

Implementing SSI surveillance using CDC criteria is known to be more sensitive compared to other surveillance methodology (Gibbons et al, 2011), especially with respect to the diagnosis of superficial SSI. As more than 80% of SSI in this cohort was in the superficial category it is possible that SSI may have been over-diagnosed in comparison, especially in those cases where there was an absence of positive microbiology and where the post discharge diagnosis of SSI was included in the analyses.

Both bypass and non-bypass operations were included in this analysis, as previous work with respect to postoperative complications after PCS by Agarwal et al (2014) had determined rates of sternal wound infection to be similar between these groups (2.2% versus 1.8% respectively). Previous studies specifically investigating cardiopulmonary bypass related SSI further increase heterogeneity and may contribute to underreporting of SSI (Mehta et al, 2000; Allpress et al, 2004; Nateghian et al, 2004; Sarvikivi et al, 2008). These factors demonstrate the potential difficulties when trying to use SSI data to compare rates between institutions, previously reported by Singh et al (2015), after identifying coding, data extraction and patient selection errors in SSI data submitted for mandatory surveillance following orthopaedic surgery; persisting despite the use of a defined methodology (PHE, 2013), and raising concerns over the validity of using this data for benchmarking purposes.

Consequently, the rate of SSI reported in this study should be interpreted with caution, and, due to the methodological decisions made in the conduct of this study it is unlikely to be comparable to other units reporting SSI outcome.

3.6.2 Risk factors for SSI

3.6.2.1 Neonates

Neonates in this study were found to have a substantially higher risk of infection than any other age category even after adjusting for other prognostic variables. This finding is consistent with previously published work in the field (Barker et al, 2010; Costello et al, 2010; Sarvikivi et al, 2008; Allpress et al, 2004; Mehta et al, 2000) and can be explained by the relative immaturity of immune and other end-organ systems (McCance & Huether, 2006). Physiological immaturity of the renal system, in addition to the known risk of transiently diminished renal function following exposure to cardiopulmonary bypass (Dent & Schwartz, 2009), predisposes neonates to substantial fluid shifts from intravascular to extracellular

compartments ('third-spacing') both intra- and postoperatively. This combined with a thinner outer epidermal layer compared to adults (Dyer, 2013) only loosely bound to the dermal layer (McCord & Levy, 2006) may increase both the risk of wound dehiscence and related wound infection. Previously, the actual SSI risk of neonates had not been quantified in the research literature, as this age group have often been excluded from studies precisely because of these complexities of physiology (Stey et al, 2014). This work demonstrates that even when adjusting for other risk factors, neonatal age is a highly significant risk factor for SSI. Furthermore, as any surgery undertaken within the first few days or weeks after birth is usually life-saving, age is rarely a modifiable SSI risk factor. Mitigating risk, therefore, must come via other strategies for the neonatal age group.

3.6.2.2 Weight-for-age *z*-scores

Although weight-for-age *z*-scores remained a predictor variable through each stage of the regression analysis, the results of this study did not show an association between being underweight and greater risk of developing SSI. Conversely, the results suggested the relative risk of developing SSI in the underweight group was lower than those in a normal or overweight category. Furthermore, the direction of this effect persisted across all but one of the age categories as demonstrated following WAZ-Age interaction modelling. As this finding was unexpected, contributing factors and potential explanations are discussed here in detail.

3.6.2.2.1 WAZ in neonates

Out of the 148 included neonates the incidence of WAZ scores less than -2 SDs was 12% providing evidence that cardiac babies are generally born at normal weight which is consistent with recently published literature by Story et al (2015) demonstrating only 17% of neonates antenatally diagnosed with congenital heart disease were associated with a birth weight centile <10 when standard population centiles were used.

Findings are inconsistent with Malik et al's (2007) large case-control study which reported babies with congenital heart disease are twice as likely to be born small for gestational age compared to control subjects (adjusted odds ratio 2.09, 95% CI, 1.78 – 2.46). Additionally, Petrossian et al (2015) reported a higher incidence of both prematurity and foetal growth retardation in cardiac infants compared with normal controls. Petrossian et al (2015) reanalysed historical birth weight data from 1981-1989 comparing babies with congenital heart disease with their normal counterparts. The largest average birth weight deficit between the two groups (-265g) were in babies with endocardial cushion defects (e.g. complete atrio-ventricular septal defect) associated with Trisomy 21 (Down's syndrome). Birth weights in the cardiac babies were consistently lower across six other diagnostic groups, with only

transposition of the great arteries (TGA) showing no statistically significant difference to the birth weights of the control babies.

However, extrapolating data from Petrossian et al's study and applying WHO (2006) WAZ criteria, all babies were classified within a normal weight-for-age category, with the net difference between mean and -2 SDs being 800g. Therefore, despite a shift towards the lower end of norm, cardiac babies still remained within the normal weight category. In summary, therefore, it appears the pathophysiological association between congenital heart disease and foetal growth remains uncertain. A normal WAZ score at the time of surgery in this study's neonatal population is more likely to be a reflection of maternal characteristics known to affect birth weight (such as weight and height, parity, and ethnicity) as reported by Story et al (2015) with unaffected intra-uterine growth and development as opposed to being reflective of nutritional status. As for the most part, serious structural heart disease is completely compatible with foetal life and it is not until after birth that postnatal alterations in cardiopulmonary haemodynamics result in physiologic instability (Barry & Thureen, 2016). This goes some way to supporting this observation.

It is recognized that due to a combination of expected post-partum weight loss and early surgical intervention, the true relationship between WAZ classification and risk of SSI in this study population may have been distorted. The lack of opportunity for critical neonates to lose weight due to their cardiac condition prior to time-critical surgery and may have confounded any association between being underweight and SSI in this high-risk age category. In addition, by using a surgical database as the primary source of participant identification this study is unable to take account of the number of low-birth weight babies who did not reach operation. As data were confined to only those neonates who underwent surgery it does not take account of those low-weight babies who had surgery postponed whilst allowing them to grow; who died during this growing period; or who did not survive to term (e.g. maternal choice of termination of pregnancy for hypoplastic left heart syndrome). However, findings suggest that cardiac neonates may not have opportunity to develop significant illness-related weight loss prior to surgery.

3.6.2.2.2 WAZ in infants

The highest incidence of low WAZ scores was found in the infant age category, with almost half of them being in an underweight category. A subset of low birth weight neonates left to grow prior to surgical intervention would also have been subsumed into this age category, which may have contributed to the exponential increase in the number of underweight infants. It is impossible to determine if these low-birth weight babies were exposed to additional care

interventions during this growing period in hospital, which may have an unknown and unmeasured impact on their overall SSI risk.

Findings suggests that the phenomenon of poor growth in cardiac children does not appear until infancy, previously reported as a period when the pathophysiological changes of their cardiac malformation will occur, and faltering growth is known to be the common presentation in this age group (Noble et al, 2010). The study findings are in keeping with the low weight and stunting associated with congenital cardiac malformations and provides a plausible explanation for the low incidence of neonates in an underweight WAZ category found in this study.

3.6.2.2.3 WAZ in older children

For children over 1-year of age, 40% were reoperations, which likely represent the subset of children on a palliative surgical course rather than a corrective one, and who are known to be at risk of faltering growth (Anderson et al, 2011). Although growth and development may continue satisfactorily on the same trajectory throughout childhood, these children are known to be of lower weight when compared to their normal healthy counterparts (Marino & Magee, 2016). This study failed to incorporate nutritional interventions (e.g. tube feeding, high-energy formula) that may particularly be supporting weight gain in these children, which again may be a factor distorting the true relationship between WAZ, reoperation and WAZ.

3.6.2.2.4 Summary

Overall this study classified 28% of the sample population as underweight, whilst only 1.5% were classified in an overweight category. The persistence of the protective effect of low WAZ across most of the age categories does suggest that being underweight *per se* does not impact on risk, and that it may be achieving an overall increase in growth trajectory that may be the more important factor. This would align with Eskedel et al's (2008) finding that it was a failure to grow that was associated with poorer long-term outcomes after cardiac surgery. This raises an interesting question as to whether cardiac children are better at coping with being underweight, or whether they grow optimally for the limitations imposed by their cardiac condition. As catch-up growth has been demonstrated in most children once they have had surgical correction of their congenital heart condition (Knirsch et al, 2010), it does suggest that poor growth is more related to the increased demand placed by their heart failure, rather than by any intrinsic defect caused because of the condition.

In addition, traditional standardized weight for age *z*-score categories may not be sensitive cut-off points for children with cardiac conditions, as distribution within the categories demonstrated a leftward skew with far greater numbers of children in the low weight

percentile than high weight percentile. This finding is similar to those of Stey et al (2014) who also found younger children undergoing non-cardiac surgery appeared more likely to be of low weight, which should not be the case were the sample studied perfectly representative of the reference census data population. This suggests that either reference data may no longer be representative of childhood growth patterns, or alternatively, that the population studied by Stey at al (2014) may have included a higher proportion of children with co-morbid conditions which are known to adversely influence growth.

Although it is well accepted that poor nutrition in childhood will result in poor growth, with weight gain being the most commonly used method of assessing this in childhood, the reverse situation, that poor growth is due to undernutrition may not hold true especially in a cardiac population. The relative absence of children in the overweight WAZ category implies that using a solely weight-based marker as a means of identifying undernutrition in this study may not be a sensitive measure in identifying which children are at nutritional risk. However, as identified by systematic review there is a lack of reliable, sensitive, non-anthropometric markers in use (Hill et al, 2016). The protective relationship between low WAZ and SSI observed in the neonatal and younger child population was unexpected. This would suggest that postoperative variables not included in the analysis may be exerting more of an influence on SSI, or the omission of an unmeasured preoperative factor may have been important. As neonates were most at risk, any unmeasured influences may be exerting more of an effect within this age category.

3.6.2.3 Cardiac reoperation

Despite strict methodological criteria excluding any patient having had cardiac surgery within the previous 12 months, an association between prior cardiac surgery and risk of SSI was confirmed in this study, as previously identified within the paediatric literature (Barker et al, 2010). Having ensured patients are free of infection from earlier surgery at study entry, this is an interesting finding and warrants further investigation. However, due to small counts within this category, it is recognised that this may be down to chance. It must be noted that this predictor variable only became significant at the model checking stage, but it did improve model discrimination. However, there is some evidence of collinearity between previous cardiac operation and haemoglobin levels, as including this variable in the model checking phase did reduce the significance of the relationship between high haemoglobin levels and SSI. Potential reasons for this are addressed further in section 3.7.2.6.

3.6.2.4 Staphylococcal aureus carriage

Results from this study demonstrate that preoperative carriage of Staphylococcus aureus (SA) irrespective of decolonisation practices, remained an independent predictor of SSI (OR 1.88,

95% CI, 1.01 – 3.52), with a relative risk almost double to that of non-carriers. This is consistent with the adult literature regarding SA carriage and increased incidence of SSI (Bode et al, 2010). However, two recent studies in paediatric cardiac surgical populations have not demonstrated similar findings. Macher et al (2017) reported no association between carriage and SSI (OR 1.03, 95% CI, 0.22 – 4.82) in a cohort of 68 patients less than 1-year (mean age 87 days, SD ± 88) undergoing bypass surgery. Reported rates of carriage (both MRSA and methicillin-sensitive SA) were 26.5% with an SSI incidence of 19.1%. Although age ranges are not directly comparable, and the small sample size limits its interpretation, there appears to be a consistent finding that neonatal SA carriage is lower than for older age ranges. Similarly, Silvetti et al (2017) studied this relationship in 169 patients less than 18-years undergoing open-heart surgery, reporting SA carriage at 50% but no association with incidence of SSI (relative risk 1.24, 95% CI, 0.64 – 2.39). Again, sample size was limited to those patients having preoperative SA screening, and thus interpretation is limited. Rates of SA carriage in both previously published paediatric studies were from Europe (France and Italy respectively) but as inclusion criteria was dependent on screening being undertaken, only 83% and 48% of operated patients were included in the analysis, which may have introduced selection bias in terms of the findings, as there may have been subtle differences in the profile of those patients screened versus those that were not.

As prolonged intensive care stays in children have been shown to increase the risk of bacterial colonization and further infection (Algra et al, 2012; Carcillo et al, 2016; Rosanova et al, 2009) routine antimicrobial washes were introduced into the paediatric intensive care unit in January 2014 (mid-way through the study). These were administered on weekdays to all children admitted to the unit, irrespective of cardiac or surgical status, in the expectation of reducing the incidence of endogenous re-colonisation, or exogenous colonisation, and to reduce the risk of healthcare associated infection, which may be life-threatening in this paediatric population. This would have been in addition to the preoperative treatment introduced as part of the cardiac surgical bundle outlined in Appendix 10. Univariate analysis did not demonstrate a significant difference in SSI rates between the year preceding and the year after this practice change (p= 0.329). These findings warrant further investigation, as they suggest one of two possibilities – firstly, that the evidence gained from adult populations regarding skin decontamination cannot be extrapolated to children; or secondly that existing decolonisation practices are not sufficiently protecting children with Staphylococcus aureus carriage against SSI. Furthermore, it is possible that extending antimicrobial washing beyond the duration of the postoperative inpatient ICU stay, or, indeed, beyond discharge until the wound has fully healed, may be of some protective benefit.

3.6.2.5 Operative team and environment

The nature of the operative team – theatre personnel as well as environment – was also shown to be associated with SSI outcome. This is consistent with earlier research in adults which suggests the most important factor in determining postoperative infection rate is surgical competence (Mishriki et al, 1990, 1991). Aspects of surgical technique – chest opening/chest closure methods, tissue handling, use of diathermy and haemostasis – are all regarded as influential in the aetiology of SSI and important aspects of surgical training (McHugh et al, 2011). It is also important to recognise, however, that some intraoperative practices (such as choice of surgical skin preparation) may be beyond the control of the surgeon and their team.

NICE guidance for reducing SSI recognises that while some patient characteristics, such as, obesity, hyperglycaemia, and malnutrition, may be modified prior to surgery, others, such as the complexity of the procedure and the underlying illness in the patient, cannot (NCCWCH, 2008). The environment of both the individual theatre and the theatre complex is rarely within the control of the surgeon. For example, during the period of study both cardiac theatres were relocated due to the requirement of essential maintenance of airflow systems and structural work. Although on univariate analysis whether the operation took place in main cardiac theatre or a temporary theatre during the period of works was not significant in this analysis, theatre airflow and exchange have been implicated as contributory factors to SSI following adult cardiac surgery (Young & O'Regan, 2010). Although evidence regarding higher levels of bacterial counts with increases in intra-operative door opening and staff movement is weak at best, it remains part of the pathway (NICE, 2013) as a recommendation for reducing SSI. However, improving intraoperative theatre practice has previously been found to contribute to decreasing SSI risk (Graf et al, 2009; Forbes et al, 2008). Quantifying the actual effect on risk reduction, however, is problematic as there is evidence that introducing such changes has no beneficial effect on SSI rates (Murray et al, 2011). However, the fact that differences in relative risk persisted within the different surgical teams despite equity of case distribution, adjustment for surgical complexity, and where intraoperative protocols are applied in line with a bundle approach is suggestive that intra-operative practice may have had an important impact on SSI development.

3.6.2.6 Preoperative serum haemoglobin levels

Children entering operation with a greater than normal haemoglobin (Hb) level for their reference age were also shown to have a significantly higher risk of infection. This may be explained by the fact that polycythaemia (high Hb levels) is associated with cyanotic heart disease; cyanosis will occur in those conditions where desaturated blood can enter the

systemic circulation without passing first through the pulmonary vascular bed (Noble et al, 2010), and is termed a right-to-left shunt.

Shunting of this nature will result in sub-normal levels of tissue oxygen tension (PaO_2). In such situations, the body compensates by increasing the production of Hb as a mechanism to improve the oxygen carrying capacity of the body. Tissue oxygen tension will remain low in comparison to normal, but this facilitates the release of oxygen at tissue level.

Cyanosis is common in those children on a staged congenital surgical pathway, whether ultimately destined for a definitive repair (that is, a serial circulation with two ventricles, each with separate venous inlet vessels and arterial outlet vessels) or a palliative one, in which stable oxygen saturations are achieved even though a physiologically normal circulation cannot be produced. For example, the circulation following a Fontan operation consists of one ventricle which has sufficient function to support systemic circulation, and where pulmonary circulation is maintained via systemic venous blood draining directly into the pulmonary arteries (Di Nardo et al, 2011).

A study undertaken in adult general surgical patients found levels of tissue oxygen tension (PaO_2) at 40 – 50mmHg were associated with a 43% rate of wound infection, compared to subjects with PaO_2 levels equal or greater to 90mmHg where SSI incidence was zero (Hopf et al, 1997). This suggests there is a threshold level for tissue oxygenation and perfusion, below which SSI risk increases. Previous reports have identified that adult cardiac and vascular surgical patients are known to exhibit markedly lower tissue oxygen tension values (25 – 50 mmHg) than adult patients undergoing other sites of surgery (Chang et al, 1983), therefore similar pathophysiology occurring within cyanotic paediatric cardiac surgical patients will likely be consistent and postulate an explanation of the increased risk of SSI. Indeed, coupled with the increase in blood viscosity associated with higher Hb levels, there may be further impairment of microvascular perfusion contributing to the increased SSI seen in this group (McEwan, 2009). Subsequently, sub-optimal blood flow through tissues and organs can increase the risk of infection complications, particularly SSI, explaining why current guidance recommends both supplemental oxygen delivery and normothermia as strategies to reduce SSI (NICE, 2013).

As preoperative oxygen saturation levels were not included as a predictor variable in this study, Hb level may be acting as a surrogate marker for cyanotic heart disease, reflecting a state of hypoxaemia and tissue ischaemia which may adversely affect mechanisms of wound healing (Ben-Ami et al, 2008; Whitney & Heitkemper, 1999). This may also explain why the significance of high haemoglobin levels was significantly reduced when adjusting for other

factors, as haemoglobin level – and indeed preoperative oxygen saturation levels – are likely to be highly correlated with previous cardiac operation. In view of this finding, it is important that future prospective studies include preoperative oxygen saturations as a potential predictor variable when considering SSI risk, and any collinearity with previous cardiac operation is explored.

3.6.2.7 Case complexity

Surgical case complexity, although achieving significance in univariate analysis, did not persist as a factor associated with SSI development during multivariate analyses. The Basic Aristotle Score (BAS) was utilised in this study to quantify surgical case complexity, univariate for patient-related factors known to affect mortality and morbidity risk. The model was designed following consensus by surgeons (Lacour-Gayet et al, 2014), rather than being modelled on patient data. Although more recent risk-adjusted prediction models have been introduced (Pagel et al, 2013) primarily designed to predict mortality rather than surgical complications *per se*, there is likely to be some correlation between morbidity and mortality. However, the adjustment inherent within any model adjusting for patient related factors – of which age would be one example – would make their inclusion in logistic regression modelling methodologically problematic, therefore the univariate BAS was utilised.

Case complexity has previously been reported as an independent risk factor for SSI following paediatric cardiac surgery (Barker et al, 2010), although this has not been consistent across all studies reporting on this (Costello et al, 2010; Sohn et al, 2010). Other studies have used a severity of illness score, including the American Surgical Anaesthesiologists ASA score (Mehta et al, 2010; Sarvikivi et al, 2008) and PRISM (Pollock et al, 1990) to assess complexity, again with inconsistent results. Sohn et al (2010) included five measures of complexity/illness severity and following multivariate analysis no score was independently predictive of SSI. However, NICE (NCCWCH, 2008) identified complex surgery is more often distinguished by prolonged duration of the procedure, and a following prospective comparative study of 2345 patients undergoing coronary artery bypass grafting (Russo & Spelman, 2002), duration of surgery more than 5 hours was an independent risk factor for SSI (OR, 1.75; 95%CI, 1.18 to 2.58).

Use of cardiopulmonary bypass (CPB) failed to achieve significance on univariate analysis, although duration of CPB has been identified as a predictor in other paediatric studies (Mehta et al 2010; Kagan et al 2007) and may be a marker for both operation complexity and surgical performance. Neither deep hypothermic circulatory arrest nor delayed sternal closure were significant on univariate or model checking stages of analysis, although both have previously been implicated as risk factors for SSI outcome (Allpress et al, 2004; Pollock et al, 2010). It

must be recognised that, as with patient age, none of these intraoperative factors are likely to be modifiable risk factors in SSI prevention.

3.6.2.8 Overall assessment of the statistical model

The pseudo R-square value for the logistic regression model was 0.15 which indicated that the included variables only predicted a small portion of the observed risk. This suggests that those patient and surgery related factors which were included in the model only predicted a small proportion of the risk of SSI. As the primary data source for variables was a surgical database designed primarily to capture surgical activity, it is recognised that there may also have been important preoperative factors that were omitted from the model because they were not available, for example preoperative oxygen saturations as an indication of cyanosis or preoperative mechanical ventilation.

Due to the nature of the inclusion criteria, only factors that were known (patient-related) or predictable (intraoperative factors) were incorporated into the mathematical model. This may have prevented learning the potential significance of any early postoperative factor that might have exerted a more significant influence on SSI development. This is important, as these early postoperative factors may be important, as suggested by Pollack et al (2015) who reported the ability to predict new morbidity at discharge after 4-hours of intensive care admission. Therefore, it is likely the inclusion of postoperative variables, such as admission severity scores, inotropic requirements, postoperative bleeding requiring blood transfusion etc. may have improved the model's predictive performance, and also points to the relative importance of non-patient related factors in the development of SSI.

3.6.3 Strengths of the study

The current study identified three significant predictors for SSI within one UK single-centre providing palliative and corrective surgery for congenital heart disease in children. This was a retrospective analysis of SSI incidence and risk factors for infection over a two-year period. During the study period consultant surgical staff did not change, and there was relative consistency within the junior surgical team.

The primary benefit of using a prospectively maintained departmental database was the accuracy of ascertaining outcome, as details of the postoperative recovery including SSI complication were robustly maintained during the study period and served as the primary source of Trust-wide cardiac SSI surveillance data. This meant that a secondary process of outcome validation for study purposes was not required. During the 2-year study period there was consistency in SSI surveillance and application of agreed CDC criteria for SSI identification, with consultant level verification.

The use of a recognised, widely utilised classification system for the identification of SSI being consistently applied across the department during the time of this study is a methodological strength of the study. The CDC definition for SSI includes provision for a surgeon to diagnose SSI even in the absence of purulent drainage or positive microbiology samples. Although use of this criterion raises the potential for false-positive SSI particularly in the diagnosis of superficial SSI, the importance of including this has previously been demonstrated by Taylor et al's (1990) finding that 16% of all SSI was attributed to the judgement of the surgeon rather than from other standardized CDC criteria.

As the study was undertaken in a single-site centre, in a particularly defined sub-specialty of paediatric surgery, the study results may be of interest to other congenital cardiac centres providing a surgical service. A 20% incidence of cardiac reoperation is not uncommon for children with congenital heart disease where staged reoperation for palliation or correction is well observed, and the majority of operations occurring during weekdays is in keeping with the nature of an elective surgical programme. The fact that rates of SSI did not increase during emergency operations will be of significance to other specialties. Rates of neonatal surgery as a percentage of total operations is in keeping with high volume paediatric cardiac surgical centres across the UK (Franklin et al, 2017), reflecting a similarity of surgical cases across these units. In terms of the findings regarding SA carriage and its relationship to SSI, this particular finding is likely to be generalizable to other surgical specialties.

A total sample size of over 600 participants entering logistic regression modelling enabled the study to explore the association of SSI with undernutrition adjusting for other potential independent predictors with some degree of precision, as per Peduzzi et al (1996). The retrospective nature of the study meant that data was collected on all patients undergoing surgery, with no loss following recruitment. Additionally, there was no element of selection bias which may have been a limitation in a prospective study for parents declining consent to participate.

Due to the processes in place to check the quality and validity of the data, inputting errors or data omissions were rectified ensuring a clean dataset. With departmental processes in place to determine SSI outcome prior to the commencement of the study, ascertainment of exposure was assured which is an important criterion for cohort studies (Hill, 1965). Variables entering logistic regression modelling were reflective of those already identified from prior research, and therefore results are likely to be generalizable to other paediatric cardiac surgical centres.

Although the study was retrospective in nature, the primary data source was a prospectively maintained surgical database, therefore the likelihood of incomplete SSI ascertainment is minimal. The possibility that a case was missed is unlikely, as any patient developing SSI complications post discharge would have been referred to the surgical team.

3.6.4 Study limitations

There are several limitations to this study. The primary source of data was a cardiac surgical departmental database, which although its use enabled robust ascertainment of SSI outcome, was not specifically designed for research purposes. Therefore, although some demographic and patient data have been incorporated, the focus of the departmental database is skewed to diagnostic and operative details rather than specific patient-related factors. Consequently, the scope of the variables used as potential predictors within this study were reliant on those data routinely collected, which might mean that important data on known or unknown risk factors were not available for analysis, and limited to those items (for example, blood results and microbiology results) able to be additionally sourced from hospital information systems. This is a limitation of retrospective rather than prospective cohort studies where specific data items can be specified prior to study commencement. It is recognized that potentially important variables, such as preoperative oxygen saturation levels, have been omitted from this study. The inclusion of preoperative haemoglobin level in the final model suggests that preoperative cyanosis may be an important risk factor that should be included in future studies.

To ensure children entering the dataset were free from infection any operation on a patient having cardiac surgery within the preceding 12 months was excluded. Fortuitously, a patient level rather than operation level analysis was able to be adopted, which subsequently ensured multiple surgeries in the same patient would not be correlated. It is recognised the implication of these strict *a priori* inclusion and exclusion criteria may have led to the potential omission of those patients who would be most vulnerable to undernutrition (i.e. young infants relying on a purely milk-based diet). In addition, this may also have omitted from the study a substantial proportion of the infant workload of a typical paediatric cardiac surgical unit, which although satisfactorily ensuring children did not enter the study with a residual risk of SSI from prior surgery, may have impacted on external validity.

All quantitative variables were categorised for use in the logistic regressions. This allowed for a general shape of the response to be used since a linear response on the logit scale cannot always be assumed. Traditionally, the results of logistic regression are presented as tabulated odds ratios (ORs) and these are easy to interpret when shown for different categories of a variable. Thus, subtleties within individual variables, for example, duration of cardiopulmonary bypass, may have been lost. It is recognised that duration of cardiopulmonary bypass may act

as a surrogate marker for surgical complexity, and although use of bypass was not found to be predictive of SSI, it would be anticipated that neonates would have longer durations of cardiopulmonary bypass times. Therefore, analysis of time on bypass – or choosing a categorical cut-off – may also have been found to be predictive of SSI. The fact that other interactions other than WAZ score and age category were not explored may have resulted in potential correlation between other variables. For example, high haemoglobin levels and previous cardiac operation may well demonstrate collinearity which was not explored within this study.

The event rate of circa 12% in circa 666 observations put bounds on the numbers of factors, eight in this study, that could be included simultaneously in a logistic regression model. This is inevitable when the outcome of interest, the occurrence of SSI, is a binary outcome and not a measurable quantity. Further, any degree of association between the covariates will inevitably reduce the power of the study to detect the effects of covariates and this will have occurred in the analyses of these retrospective data. Hence it is important to be circumspect about the implications for practice which can be derived from this retrospective study.

A recent review by Gibbons et al (2011) identified wide variation in the frequency of SSI rates when using different definitions – with CDC criteria classifying over twice as many wounds infected as in comparison to using the least sensitive ASEPSIS definition. Therefore, it is acknowledged that using the CDC classification system may have led to rates of diagnosis in this study being higher than previously reported in the literature using alternative methodology, suggesting a robust, universally accepted definition for SSI is lacking, and for any meaningful future studies – especially when comparison of SSI rates is required – this would be important to address.

Finally, it is impossible to tell whether subtle changes in intra-operative technique occurred during the two-year study period, which may have impacted the results of this study. Although the overall rate of SSI found in this study is higher than published rates from other countries, comparability with other UK centres is impossible due to the absence of published SSI surveillance data within the specialty of paediatric cardiac surgery.

3.6.5 Implications of the study

3.6.5.1 Implications for clinicians

The results of this study suggest that SSI in children following paediatric cardiac surgery may not be related to undernutrition, with the independent risk factors for SSI identified in this study and amenable to modification are scarce. In addition, development of SSI may be more related to early postoperative factors, such as postoperative bleeding with the requirement for

transfusion, than to patient-related factors. This will require further attention in order to verify and identify strategies which may mitigate overall risk.

Neonates continue to be identified as being at high risk for both early mortality and SSI complications, with the suggestion of longer lengths of hospital stay than for other age groups. This remained despite adjusting for other risk factors in logistic regression modelling. Somewhat surprisingly, in all age groups, lengths of postoperative stay appeared related to category of SSI, rather than the actual diagnosis, with lengths of stays for superficial SSI not significantly longer than that without SSI. Deep and organ space SSI, although of low incidence, were both associated with significantly longer durations of hospitalization. Further investigation is certainly warranted to explore this finding further, and to identify how SSI risk may be mitigated to improve patient outcomes.

This study also demonstrates that the SSI risk following paediatric cardiac surgery can vary depending on whether a patient or operation level analysis is performed. This occurs irrespective of the diagnostic criteria for SSI used, or the robustness of data collection methodology. This study also highlights that the reporting of SSI within the surgical team is likely to lead to better detection (and therefore higher incidence) than surveillance methods which fall under the responsibility of the hospital's Infection Control team which is the common case. This has implications for any service initiating SSI surveillance which is likely to be high priority as benchmarking focused on such morbidity will have wide appeal and relevance in the face of extremely low surgical mortality (Pollack et al, 2015). Until these points are addressed, efforts towards quality improvement will be challenging.

3.6.5.2 Implications for future research

Study results have identified the current profile of WAZ scores in this paediatric cardiac population, which corroborates the lower weight reported for children with congenital heart disease and raises the question as to whether existing WAZ reference ranges should be applied to this specific population. The apparent protective effect, seen by being categorized as underweight, is an unexpected finding and certainly warrants further investigation. However, it would be erroneous to imply from the study findings that nutritional status prior to surgery is not important, but perhaps WAZ scores may not be a sensitive measure of this in cardiac children, especially when used as an absolute value at the time of surgery. It also raises the question as to how reliable a marker weight-for-age is in identifying poor nutritional status as opposed to poor growth. Due to both of these findings, a better method for assessing nutritional status in cardiac children is warranted.

Future modelling should incorporate variables of duration of surgery, early postoperative factors such as vasoactive inotrope scores, oxygenation index, feeding practices to determine the importance of early postoperative factors not considered as part of this study. Preoperative factors may not be where mitigating risk of SSI lies, and indeed some intraoperative and postoperative factors may be more important in determining SSI incidence, for example, blood transfusion volume, bleeding, and time to initiation of first postoperative feeds.

In addition, the role of previous Staphylococcus aureus carriage in the early postoperative period until wound healing has occurred has not been investigated in a paediatric cardiac surgical population. As re-colonization patterns have been identified in adults, sole attention to preoperative clearance may not be sufficient in minimising the risk of postoperative Staphylococcus aureus re-colonization and subsequent wound infection.

3.7 Conclusion

Three patient variables were identified as independent predictors for SSI in children following congenital heart surgery. The developed model was found to have an acceptable level of discrimination; however, it did not accurately predict all SSI outcome, which is likely to be reflective of the multi-factorial nature of SSI development, particularly in a sample population with wide age ranges of children with differing pathophysiology and maturity of end organ function. It may also, however, reflect the omission of important variables which were not under study.

Although weight-for-age *z*-scores were utilised as an attempt to assess nutritional status, it became clear that this fails to accurately assess nutritional status in a neonate whose weight is more reflective of foetal growth and development rather than postnatal nutritional intake. Assessment of feeding volumes might be a better way of assessing those at nutritional risk due to either poor feeding or cardiac cachexia, both of which might impact on postoperative outcome.

Further, it is recognised that early postoperative factors, such as blood transfusion requirements; timing of enteral feed initiation; and length of intensive care stay, were not considered as part of this study and these may have an important role in mitigating SSI risk. For example, length of intensive care stay, and diagnosis of other infection are two variables that might feasibly impact on SSI risk. However, the aim of this study was to focus on pre-and perioperative factors known in advance of surgery, and which may be open to modification. It must be recognised, however, that aspects of early postoperative management may also be open to modification and reduce SSI risk. For example, in a population routinely managed with

fluid restriction as part of postoperative care, the degree and severity of restriction, and time to successful attainment of enteral feeding, may be equally as important in terms of nutritional assessment and be more amenable to modification than operative weight.

From this study, it is important that any future modelling incorporates these further variables which may be predictors for SSI outcome. Of relevance, these would include duration of surgery, preoperative oxygen saturations which may impact on tissue perfusion and subsequent wound healing processes. Body temperature which, independent of whether deep cooling was used as part of the intraoperative strategy, is also a factor which warrants further investigation in this paediatric population.

In summary SSI continues to be a significant cause of morbidity in a paediatric cardiac surgical population. Understanding the risk factors for SSI development, and attempting to find and alter the impact of those factors which are potentially modifiable, continues to be an important, valuable and challenging goal in attempting to reduce SSI development in this patient group. Of interest and relevance with respect to both the high prevalence of SSI, and the complexity of assessing adequacy of nutritional status, cardiac neonates are a patient subgroup demanding additional investigation.

Chapter Four: Feeding patterns and related outcomes in neonates undergoing surgery for congenital heart disease

4.1 Introduction

In the previous chapter undernutrition as classified by weight-for-age z-scores less than -2 SDS was not found to be an independent risk factor for surgical site infection following paediatric cardiac surgery. It did confirm, however, that neonatal age was the most significant risk factor associated with SSI, and that the proportion of low weight-for-age z-scores in this age group was low compared to infants and younger children.

Findings also suggested that weight-for-age (WAZ) scores based on standard population centiles may not be a sensitive indicator of nutritional status in children with cardiac disease, who despite being within the normal curve of weight distribution, display a distribution skewed towards lower weight compared to the distribution within the general population of a similar age. As a consequence, despite the observed lack of a relationship between low WAZ and surgical site infection (SSI), nutritional status may still be of relevance in this cardiac surgical population, in particular for neonates who are known as being at most surgical risk and were identified in the previous study as being at most risk of surgical site infection (SSI). Maximum SSI risk reduction, therefore, lies in targeting this age group which has been identified as being underrepresented in previous research through the systematic review in Study One. The focus of interest for the third and final study, therefore, is the exploration using case study methodology of neonatal feeding patterns in neonates undergoing paediatric cardiac surgery, with particular interest in its relationship with postoperative outcome including infection.

This chapter commences with a brief overview of neonatal cardiac surgery and the existing literature related to the complexities of feeding in this population before presenting the results of the case study.

4.2 Background

Over a third of children with congenital heart disease require urgent care as babies, which may include open heart surgery in the neonatal period (Marino et al, 2001). Although often being of normal or near-normal birth weight many of these infants experience significant weight loss and failure to thrive while hospitalised for their surgery (Hehir et al, 2008). Poor nutrition has

been associated with longer hospital stays and infection complications in adults but, despite growth failure being prevalent in the congenital heart population (Varan et al, 1999), there are few reports of its impact on postoperative outcomes including infection complications.

Outside of adult surgical populations, evidence linking postoperative infection complications with poor nutritional status in children is weak at best. The systematic review reported in Chapter Two (Hill et al, 2016) investigating whether undernutrition was prognostic of infection complications in children undergoing surgery found weak evidence for a general association when all infection complications were combined, but no evidence for an association between undernutrition and surgical site infection. In this review, however, term neonates were under represented, highlighting a dearth of evidence in this vulnerable group.

Immaturity of organ function and complex physiology after birth make neonates unique compared with other childhood age groups (Thilo & Rosenberg, 2005; Krebs et al, 2005) often leading to their exclusion from large studies, or as in the case of Stey et al's (2014) they were excluded because of anticipated issues with statistical analysis. In addition, traditional methods of anthropometrical assessment may not be suitable for this age group, particularly when being used as a predictive indicator of undernutrition. Findings from this research to date has provided evidence that in neonates, weight-for-age assessment appears more reflective of intrauterine growth rather than nutritional status. Therefore, these measurements are unlikely to be sensitive indicators of nutrition in neonates undergoing surgery. Although anthropometry is useful for assessing longitudinal speed of growth, length is most reliable only after 2 years of age and triceps skinfold measurements have limited applicability in infants and children due to a lack of validity (Kohr & Braudis, 2010).

In the cohort study presented in Chapter Three, neonatal SSI rates were found to be higher than in any other age category although no association with low WAZ scores was found. Of interest, incidence of weight-for-age z-scores using WHO (2006) definitions undernutrition were found to be 12%, reflecting previously published rates of 10.9% for this age category in Mitting et al's (2015) study. These findings support the difficulty in using traditional anthropometry and definitions for malnutrition and applying them to cardiac neonates, suggesting alternative investigation into the nutritional status of these neonates is warranted.

Onodera's PNI, as originally reported (Onodera et al, 1984), was initially developed to identify malnourished patients with colon cancer at higher operative risk for gastrointestinal resection and anastomosis. The study concluded that patients with a score less than 40 were at greater risk of poor outcomes, asserting that the score provided prognostic information for patients with terminal cancer. Although Onodera's PNI has since been applied to adult patients with

end-stage liver disease, tuberculosis and gastrointestinal malignancy (Seok et al, 2012) it has not been validated for use in the paediatric population. One study by Wakita et al (2011) investigated its potential application to children less than 18 months undergoing cardiac surgery and reported that a score below 55 was associated with increased length of postoperative stay. As PNI can be easily calculated from both serum albumin and total lymphocyte count, both of which have been previously linked with postoperative complications in children undergoing cardiac surgery (Leite et al, 2005; Cabrera et al, 2009), it makes this an attractive a simple test which can be calculated from routine preoperative screening tests without the need for additional sampling.

Following neonatal cardiac surgery, the evolution or acquisition of feeding skills, and their timeline during the entire postoperative stay, has not been well described. Sables-Baus et al (2012) retrospectively studied predictors of oral feeding outcome in 56 neonates surviving cardiac surgery, identifying that almost half required a feeding tube at the time of hospital discharge, with none being solely breastfed. They found predictors of oral feeding success to be shorter time from surgery to first oral feed, a larger amount taken at first oral feed and shorter duration of aortic cross-clamp time during surgery (likely a marker of lower surgical complexity). This study looked at postoperative feeding outcomes only, demonstrating a bleak picture of oral feeding success. Similarly, Nicholson et al (2013) retrospectively studied the caloric intake of postoperative cardiac neonates during their intensive care stay, concluding actual caloric intake during the cardiac intensive care unit stay was substantially below recommendations, and associated with a degree of weight loss more than would be expected during the first two weeks of life. The subsequent evolution of feeding skills and weight gain following ICU discharge in this population were not studied and adverse outcomes were not reported.

Many factors can affect feeding strategies in the postoperative period, which will of course influence feeding related outcomes. These studies clearly demonstrate why feeding difficulties have been identified as being a particularly challenging aspect for parents caring for infants following their cardiac surgery (Brown et al, 2016). So much so, feeding algorithms and guidelines have been introduced, particularly for neonates before or after entering a single ventricle surgical pathway (del Castillo et al, 2010; Carpenito et al, 2016; Braudis et al, 2009; Toms et al, 2015). Preoperatively these neonates are duct-dependent whereas, postoperatively, both pulmonary and systemic circulations are shared from one pumping chamber, perfusion to the gut can be compromised and risk of NEC is felt to be higher. Although generic intensive care unit feeding guidance exists at the study hospital, this is not

specific to cardiac neonates, and outside of the ICU, no formal guidance exists for the cardiac ward caring for these neonates before and after surgery.

Complex and high-risk surgery at this age results in cardiac instability throughout the early postoperative period, which is a contraindication to enteral feeding (del Castillo et al, 2010; Braudis et al, 2009). In consequence, the initiation of enteral feeds is delayed. Concerns over compromised gut perfusion due to the anatomical malformation limits enteral feeding both pre- and post-operatively to the extent that some neonates may never experience oral feeding prior to surgery (Jeffries et al, 2006; Slicker et al, 2013). Additional concerns over recurrent laryngeal nerve dysfunction or gastroesophageal reflux disease in cardiac neonates will mean that in addition to fluid and feed restriction as a part of early postoperative management, neonates remain vulnerable to undernutrition (Mehta et al, 2012). There is currently scant evidence regarding best nutrition practices for these critically ill infants (Hamilton et al, 2014).

A recent multi-centre randomized controlled trial concluded that early parenteral nutrition (PN) – defined as PN administration within the first 24 hours of paediatric intensive care (PICU) admission – was associated with poorer outcome than when PN was withheld during the first week of PICU stay (Fivez et al, 2016). Term neonates accounted for 14.5% of the total study population, with primary outcomes of incidence of new infection and adjusted duration of PICU dependency. All included centres were using early PN as part of standard PICU care, and post-hoc subgroup analysis of all included neonates demonstrated an odds ratio for new infection of 0.47 (95% CI 0.22 – 0.95) and a hazard ratio for earlier live discharge from PICU of 1.73 (95% CI 1.27 to 2.35). Although just under 48% of total study population were admitted following cardiac surgery, the number of cardiac surgical neonates was not reported. Even though PN administration within 24 hours of admission is not typical of most PICUs (Mehta, 2016), this research strongly supports the establishment of early enteral nutrition, which has benefits over and above those related to gut protection during periods of critical illness (Neu & Bernstein, 2006).

As mortality is known to be higher in premature and low birth weight term babies weighing below 2.5kg at the time of cardiac surgery, delaying operation until weight and post-gestational age increases remains common practice (Alsoufi et al, 2014; Kalfa et al, 2014; Reddy, 2013). However, the evidence suggests in babies born at term and of normal weight 30-day surgical outcomes have improved considerably (Brown et al, 2016), although it remains suggestive that failure to gain weight after surgery may be an important indicator of longer-term outcome. Eskedel et al (2008) found an association between impaired weight gain after congenital heart surgery and late death (defined as death after the first 30 postoperative days) in their 1:1 nested case control study of 74 children. A decline in weight-for-age *z*-score of -

0.67 (that is, falling below one percentile line) from last cardiac operation was associated with an odds ratio for death of 13.5 (95% CI 3.6 – 51.0). Mitting et al (2015) found a similar association between low WAZ and increased duration of ventilator support, longer intensive care stays and increased 1-year mortality in 248 neonates following congenital cardiac surgery.

The existing evidence demonstrates that neonates with congenital heart disease face significant obstacles to achieving enteral feeding after surgery (Brown et al, 2016), and the risk of requiring feeding via nasogastric or gastrostomy tube at time of hospital discharge is high (Sables-Baus et al, 2012). The relationship between feeding difficulties and adverse clinical outcomes is likely to be complex, however, to date, the trajectory of feeding acquisition in a group of neonates has not been explored prospectively.

4.3 Aims and objectives

4.3.1 Aim

The aim of this study was to explore the relationship of postoperative feeding patterns with postoperative outcome, including infection, in a high risk paediatric cardiac surgical population.

4.3.2 Study objectives

The objectives of the study were to:

1. describe the trajectory of postoperative enteral feeding in cardiac neonates during hospitalisation for surgical correction or palliation of congenital heart disease, including barriers to feed progression

2. establish if a relationship exists between feeding pattern and postoperative complications, including infection

3. explore the usefulness of Onodera's Prognostic Nutritional Index score (Wakita et al, 2011) in preoperatively identifying neonates who experience worse outcomes after surgery.

4.4 Methodology

4.4.1 Study design

A prospective exploratory single case study of postoperative enteral feeding in term neonates undergoing congenital cardiac surgery was undertaken to capture and describe characteristics of feeding (oral, enteral and parenteral) and growth parameters throughout hospital admission.

Case study methodology was chosen to capture the complexity of postoperative enteral feeding in this specific group of patients and enable understanding of neonatal feeding within the context of a real-time clinical setting.

Case study methodology is a preferred research strategy when 'how' or 'why' questions are posed, particularly when the researcher has little control over the course of events or when the focus of study is on a contemporary phenomenon within a real-life context (Yin, 1994). Simons (2009) further defines the case study method as enabling an in-depth exploration of the complexities and uniqueness of a particular system in a 'real-life' context, with the primary purpose being to generate in-depth understanding of a specific topic to generate knowledge or inform professional practice.

In this case study, postoperative neonatal feeding is the phenomenon of 'intrinsic' interest (Stake, 1995) in so far as the when and how neonates achieve feeding targets may have some relationship with longer term outcome. Through a holistic description and analysis of neonatal feeding experiences, the particularities of this phenomenon and its potential relationship with postoperative outcomes can be explored (Merriam, 1988). Relationships between feeding, postoperative complications and feeding success (as indicated by weight status at hospital discharge) will be considered. This is of particular interest in this group of neonates as they have previously been identified as being at risk for both high-operative mortality and postoperative complications.

As postoperative enteral feed progression and weight gain is known to be challenging, an increased understanding of how neonates are fed after surgery – with an exploration of feeding outcomes beyond the intensive care stay – aimed to reveal patterns that may be of importance with respect to longer term feeding and postoperative outcome.

For this study, therefore, the case was defined as 'postoperative neonatal feeding' and was represented by the small cohort of individual neonates undergoing cardiac surgical procedures during the defined study period, comprising the individual sub-units for analysis. A prospective design allowed the contemporaneous collection of secondary data during the inpatient stay, and through the use of documented observations and hospital charts and patient-related records, real-time follow-up and progress of physiological status with simultaneous feeding achievement could be captured and ensured that no data were lost.

The contextual boundaries of the case were set to the single surgical centre performing the surgical operations and consisted primarily of the intensive care unit and critical care areas (high dependency and cardiac ward) into which the neonates were admitted as part of routine postoperative care following transfer from intensive care. In addition, the existing intensive

care unit enteral feeding guidance (Appendix 13) needed to be considered due to its impact on decisions made regarding withholding or progressing enteral feeding volumes and acted as an additional contextual boundary. This enabled a full understanding of how neonates were fed within this single surgical centre, and identified the problems encountered during subsequent hospitalization after surgery.

4.4.2 Method

The process of understanding postoperative neonatal feeding in neonates after cardiac surgery was the intrinsic focus of interest in this study. There was an expectation that there would be an interaction between this and the context of care delivery and illness severity. The overarching aim of the study was to detail the particularity and complexity of enteral feeding in order to enhance understanding of the activity within the important contextual circumstances of hospitalization, and how this may link with postoperative outcomes.

A quantitative method of data collection was chosen, using secondary data documented as part of the inpatient record, as it would be able to provide detailed information regarding patient-status, providing an indicator of both severity of illness of the included neonates, and to contemporaneously capture enteral feed delivery and overall feeding progression, as it would be more focused and would be less subjective than other data collection strategies such as interviewing. Consideration was given to both individual and shared characteristics of the included neonates, in terms of illness severity and feeding, which provided an understanding of feeding activity within the context of clinical care. This aimed to generate themes or hypotheses which may be important for any future definitive research on this topic.

Data were retrieved from patient observation charts, fluid balance charts, hospital information systems and medical/nursing notes, reflecting documentation processes within the individual clinical areas. Intraoperative data variables (duration of surgery, antibiotic use, blood product administration) were collected from the anaesthetic chart. PICU data variables were collected from computerized hospital information systems and ICU charts. Post-ICU discharge data were collected from medical and nursing care notes within the hospital information system.

For the purpose of this study, feed disruption was defined as days on which enteral feeding was stopped for any duration within the same 24 hour period. This was then compared to days when enteral feeding continued without stoppage during the hospital length of stay or to completion of follow-up, whichever occurred first.

Using the feeding experiences of the included neonates both individual and group data were analysed, enabling the identification of both shared and unique characteristics which accounted for differences in feeding achievement and outcome between them.

4.4.2.1 Study definitions

Baseline goals for nutritional intake were defined from existing research, and for the purposes of this study minimum nutritional intake values for neonates in ICU following cardiac surgery were defined as 55 kcal/kg/day (Teixeira-Cintra et al, 2011), and full nutritional requirement was defined at or greater than 120kcal/kg/day (Ridout & Georgieff, 2006).

All neonates were classified as: i) small for gestational age; ii) appropriate for gestational age; or iii) large for gestational age based on existing curves (Battaglia & Lubchenco, 1967) in addition to classification of weight for age z-score at operation.

Cardiac lesions were categorised into one of four diagnostic classes using an anatomic classification, previously shown to correlate with mortality risk (Clancy et al, 2000). These were: a) two complete ventricles, no aortic arch obstruction; b) two complete ventricles with aortic arch obstruction; c) univentricular heart, no aortic arch obstruction; d) univentricular heart with aortic arch obstruction. The full diagnosis of each included neonate can be viewed in the relevant section of Appendix 15 (Neonatal chronologies).

Predicted risk of operative mortality was classified using the Partial Risk Adjustment in Surgery model (Pagel et al, 2013). Percentage risk was stratified into the four categories as used in this model; less than 1%, 1 – 3 %, 3 – 10%, greater than 10%. Paediatric Index of Mortality 2 (PIM2) was used to assess the percentage likelihood of death at the time of intensive care unit admission (Slater et al, 2003).

Respiratory support was defined as days on mechanical ventilation and/or invasive continuous positive airway pressure, both of which are a requirement for an ongoing level of intensive care support.

Using physiological data (vital signs and laboratory results) ongoing daily assessment of critical illness severity was judged according to the following parameters: oxygenation index (OI), vasoactive inotrope score (VIS) and ongoing requirement for ventilator and/or circulatory support. OI reflects the intensity of ventilatory support required to maintain adequate oxygenation (that is, the lower the OI value, the higher the oxygenation level is (PaO_2) at the lowest FiO_2; OI values of 0 - 25 have been associated with shorter durations of mechanical ventilation, although it is less reliable as a predictor of mortality (Trachsel et al, 2005). OI values over 40 are generally indicative of the need for extra-corporeal membrane oxygenation (ECMO). VIS reflects the level of cardiovascular support to maintain adequate blood pressure and end-organ perfusion (Wernovsky et al, 1995), attributed to a group (1-5) as outlined in Gaies et al (2014), with group 5 indicating the highest level of cardiovascular support.

Fluid balance was obtained from the bedside fluid chart, which included maintenance fluids, fluid boluses, blood and blood component products, medications and enteral and/or parenteral feeds. It also included recordable output such as urine output, chest and peritoneal drain losses, and nasogastric aspirates. The postoperative intravenous fluid regime used on the unit is 25% of maintenance fluids on day of operation, increased daily by 25% per day until 100ml/kg/day is reached on postoperative day 3. Enteral feeds, when provided, are included in this fluid restriction, unless deemed 'trophic' – that is, small amounts of feed at 1-2ml/kg having minimal nutritional value but administered as a gut protection strategy.

Postoperative complications were categorised as early or late, with the following definitions. Early complications for this neonatal cohort were defined as those occurring on the day of surgery up to postoperative day 4, with late complications occurring at any point thereafter during the follow-up period. These timings were chosen based on previous departmental audit data relating to average neonatal postoperative intensive care length of stay, informed by Study 2.

There is no standard definition of postoperative bleeding that is universally applied in paediatric cardiac surgery (Bercovitz et al, 2017). However, since neonates are at significant risk for postoperative bleeding due to: immature coagulation systems; long bypass times at low temperature; and a cardiopulmonary bypass circuit prime volume often larger than their circulating volume, basing a definition on neonatal specific data was prudent. Major bleeding was defined as blood loss greater than 65ml/kg in the first 24 hours after surgery. This definition was chosen as recent study in neonates following cardiopulmonary bypass surgery identified volumes in excess to be associated with longer duration of mechanical ventilation and ICU stay (Guzzetta et al, 2015).

4.4.3 Study site

The study was conducted in a single-site tertiary centre performing neonatal congenital cardiac surgery in England. The Heart Centre is the regional referral centre for the treatment of congenital heart defects, with a catchment area of 7 million people.

There are three full-time Consultant Cardiac Surgeons performing an annual average of 400 cases/year of both open and closed paediatric heart surgery. There is an established neonatal cardiac programme with approximately 65 operations per year, treating the full spectrum of complex congenital heart disease including the Norwood procedure as part of the surgical management for hypoplastic left heart syndrome.

The service is supported by the Paediatric Intensive Care Unit (PICU), a 23-bed unit and designated Lead Centre. It provides care for children (up to 16 years old) from all specialties

There are over 160 nurses working on the unit, ten consultant intensivists, specialist physiotherapists, specialist dieticians, pharmacists, and a team of rotational doctors in PICU, paediatric and anaesthesia training. The PICU dedicated specialist dieticians review all new admissions and advise on minimum feeding requirements and feed advancement. In those children where feeding intolerance has been identified individualized feeding advancement regimes are devised to optimize nutritional status.

The cardiac ward is a 24-bedded unit providing specialist cardiac care for children with medical or surgical conditions related to congenital or acquired heart disease, both pre- and postoperatively. There are eight consultant paediatric cardiologists and approximately 60 ward nurses. The service is supported by a team of six cardiac nurse specialists, a ward-based pharmacist and clinical psychologists. A dedicated ward-based dietician continues to review feeding and growth of all inpatients, and again, where required devise individual feeding plans for any child not receiving full enteral feeding volumes, demonstrating feeding intolerance, or for those children with feeding tubes in situ or where growth failure has been identified. If feeding is an issue at time of discharge, liaison with local dietetic teams is arranged.

4.4.4 Recruitment and duration of follow up

Recruitment occurred over a 4-month period (February – May 2017). All neonates undergoing surgery were assessed for eligibility between hospital admission and to the surgical team's decision to accept for surgery. It was estimated from prior study (Stage 2) that approximately 10-15 neonates would present for surgery within this time frame, which was considered to be a sufficient number for a case study.

Extrapolating from findings in Study 2, the median length of stay for eligible neonates was 13 days (IQR 8, 25) which is in keeping with median length of stays recently reported in the literature for neonates following cardiac surgery (Costello et al, 2014; Kumar et al, 2014). A six week follow up period, therefore, would include the 90th percentile for neonatal length of stay. Therefore, the endpoint for each included neonate was hospital discharge, death or follow-up for six weeks from the day of surgery.

4.4.5 Eligibility criteria

4.4.5.1 Inclusion criteria

1. Term neonates undergoing surgery, with or without cardiopulmonary bypass, for palliation or correction of congenital heart disease via midline sternotomy incision.
2. Operation during primary hospital admission

4.4.5.2 Exclusion criteria

1. Diagnosed infection at the time of surgery

2. Gestation less than 37 weeks

3. Neonates transferred from another PICU/NICU after more than 7 days of invasive ventilatory support

4. Pre-operative gastro-intestinal system comorbidity (e.g. Hirschsprung's disease, imperforate anus) which precluded the provision of enteral feeds.

4.4.6 Data collection

Field work took place over a six-month period[2] allowing sufficient follow up for anticipated lengths of stay. Data collection occurred three times a week contemporaneously during the inpatient stay, judged by the researcher to be sufficient to ensure the robustness of data capture, and feasible in terms of the available research time of the primary researcher. The interval between data collection episodes was flexible, dependent on the number of neonates under follow-up at any one time and other commitments of the researcher. It also ensured the researcher involved in data collection was not involved in any clinical decision making regarding feeding during active periods of data.

Patient-level data recorded by nursing and medical staff as part of routine clinical care was retrieved from hospital charts, written records and documentation, and did not involve the collection of additional data from neonates, parents or staff. This secondary data method provided the ability to objectively capture the details and nuances of neonatal feeding patterns and distinguish the trajectory of enteral feeding achievement and associated feeding disruptions. A patient-specific data collection form was used throughout the neonatal hospital stay to optimise data accuracy, prior to transcribing data into an Excel spreadsheet for data analysis purposes.

The data collection form was developed during the protocol-writing stage, with amendments made as required as the protocol evolved. Prior to active data collection, the form was piloted on one cardiac surgical neonate, with minor refinements to fluid balance criteria required, to ensure full data capture. The final data collection form (see Appendix 15) was then deemed able to retrieve sufficient patient data to enable later categorisation of patient status and severity of illness throughout the follow up period, as well as being able to quantitatively 'observe' feeding progression and relevant decision-making regarding feeding.

Various enteral feeding data points were extracted, including days to enteral feed initiation after surgery, percentage of prescribed feed delivered per day, number of days on which enteral feeds were disrupted, and complications associated with feeding. Oral feeding achievement data were extracted, either as oral amount achieved via bottle as a percentage of

[2] Please see section 4.4.8.3 for further details

total enteral feeds per day, or as breast feeding episodes with or without tube feed supplementation. Nutritional data collected included type of nutrition (enteral/parenteral), type of milk (breast/formula), feeding volumes, and trophic feeding volumes.

Both nutrient and non-nutrient volume administration was recorded, and calculated as a percentage of daily fluid intake. A weight-based fluid overload calculation (Wilder et al, 2016) was utilised as an assessment of total fluid balance for neonates nursed outside of the intensive care unit when input/output charts are not strictly maintained.

Any clinical procedure or adverse event, such as extubation or cardiac arrest (see Appendix 3 for a full list) impacting on the decision to start or withhold enteral feeding was extracted during chart review, with corresponding physiological parameters, laboratory or radiological findings, and any documented clinical assessment (medical and nursing). Confirmed or suspected infection-related complications were extracted, along with associated days on which antiobiotc treatment was administered.

At all data collection points, central venous access days, newly diagnosed infection (defined and documented using CDC criteria and treatment undertaken), along with other pertinent data were extracted.

Weight at hospital discharge was used to calculate variation from birth weight and variation from pre-operative weight as an estimate of cumulative weight change during hospitalisation. Lowest recorded weight during hospitalisation was also recorded to calculate maximum growth velocity during hospitalisation.

4.4.7 Data analysis

Given the exploratory nature of this study, analysis was focused on the descriptive and narrative interpretation of results since definitive inferences were not appropriate due to the small sample size and resulting lack of power. The level of daily detail captured during data collection episodes contributed to a comprehensive clinical dataset which provided an indication of illness severity, the nature and speed of progress during their post-operative recovery with recording of critical events or complications, and a simultaneously evolving picture of enteral feeding progress.

From the wealth of daily physiological and feeding data captured, a process of data transformation enabled the extraction of key data during the entire hospitalisation along with feeding-related data, facilitating the generation of a chronological summary for each included neonate which can be viewed in Appendix 16. The process of transforming the data in this way was to determine the temporal sequence of the neonate's hospital experience, a perspective proposed by Wolcott (1994). This enabled a way to incorporate the cardinal events or

circumstances having the greatest impact on feeding, identified through the quantitative data collection method, to be described and explored narratively. Chronology was chosen as a mechanism to aid data analysis as each neonatal journey would have an obvious beginning, middle and end, with the natural progression of enteral feeding increasing with time.

From the individual neonatal chronologies whose feeding experience comprised the units of analysis patterns of postoperative enteral feeding progress were identified. These patterns were subsequently defined as 'minimal interruption', where full enteral feeding was re-established within 7 days of surgery; 'moderately interrupted', where full enteral feeding was re-established 7 – 14 days after surgery; and 'highly interrupted', when full enteral feeding was unable to be established until or after 15 days from surgery. The final category was the absence of any postoperative feeding of nutritive value (as opposed to trophic enteral feeds). This categorical framework facilitated the narrative comparison of similarities and the ability to distinguish differences between neonates feeding experiences, permitting conclusions to be drawn which enhanced understanding, and provided rigour to the analytic inquiry. This search for 'happenings' and an understanding of complex interrelationships among all that exist distinguishes the case study from more quantitative causal methodology (Stake, 1995).

The chronologies were ordered by number according to when the neonates were recruited into the study (N1, N2, etc.). Once all chronologies had been compiled, descriptive analysis using summary statistics was used to explore overall characteristics of the included neonates, and ensure full consideration was given to the potential influence broader demographic or diagnostic variables may have had on enteral feeding progression. This aimed to potentially reveal further patterns that might have been lost in a purely narrative chronological analysis and facilitate the generation of meaning. In addition, it served to identify any neonate who may have been significantly different in either demographic or operative experience, and which would need to be taken account of in any comparison or contrasting of the individual chronologies. Both methods assisted with the identification of those unusual or particularly complicated postoperative stays, and enabled consideration to be focused on the potential impact these additional factors might exert on enteral feeding progress – of particular *a priori* interest were feeding attainment, perceived barriers to feeding (including feed disruptions), and overall postoperative growth velocity to the time of hospital discharge.

This progressive focusing within the data analysis stage, where objective clinical data were transformed into neonatal chronologies and the subsequent coding categories outlining feeding success, enabled the identification of the issues from which the themes and patterns for analysis emerged (Parlett & Hamilton, 1976). Through gaining the contextual and

chronological insight into individual enteral feeding experiences, the issues and complexity were more easily identified for further consideration and interpretation.

Finally, an evaluation of Onodera's Prognostic Nutritional Index score (Wakita et al, 2011) was undertaken as a potential screening tool specifically for cardiac neonates. In conjunction with the calculated Onodera's PNI, consideration was given as to its usefulness in identifying the likelihood of a positive feeding outcome or postoperative complication in the included neonates.

4.4.8 Ethics

4.4.8.1 Ethics approval

As the study did not involve additional risk to patients, or additional procedures or alterations in care delivery for the neonate or members of the clinical team (nursing or medical) it was judged as audit activity using Health Research Authority online decision-making tools (www.hra-decisiontools.org.uk). The study was therefore registered and accepted as an audit by the Trust's Clinical Audit Department, Audit No: 5373, and granted ethics approval by the Science Technology, Engineering, Medicine and Health ethics Committee, University of Central Lancashire (STEMH 591, Appendix 14).

The protocol stated that if concerns arose regarding the clinical care provided by health care professionals to patients and/or parents, it would be brought to the attention of the relevant clinical line manager. If the immediate safety of a patient were to be at risk during any period of data collection, the primary reseracher was to intervene in a clinical capacity and ensure the best interests of the child. If other concerns were to arise regarding the researcher vs clinician role, they would be promptly brought to the attention of the wider research team for further discussion.

Early in the data collection period the primary researcher observed not all neonates were being weighed on the day of hospital discharge, as part of the standard discharge procedure for all patients on the cardiac ward. Following discussion with the research team, and the potential implications this may have for both the neonates and the integrity of the study where weight on discharge was a data collection point, it was agreed that this finding would be fed back to the ward's senior nursing team, and the opportunity to improve practice that this presented would be taken. Consequently, where weight on day of discharge was unavailable, the last recorded weight prior to discharge was taken as the final data point.

4.4.8.2 Consent

The current cardiac surgical consent process for surgery includes using data for audit and research purposes, and states "prospective and retrospective anonymized patient data is used

for regular internal audits conducted or approved by the cardiac surgical team. The information is also analysed for local, national and international presentation and publication". This was recognised as being implied consent for this data-based project, with the project lying within the agreed parameters of this implied consent process.

This study was limited to the analysis of patient-level data previously recorded by nursing and medical staff as part of routine clinical care. It did not require any additional data to be collected from parents/carers/clinicians. Consequently, explicit consent was not required.

4.4.8.3 Data protection

Each participant was assigned a Study ID, and thereafter all data extraction forms and participant datasets were identifiable by this. This meant only the researcher at the study site was aware of participant identity during the period of data collection. From thereon in, individual patients were de-identified (i.e. a reversible process in which identifiers are removed and replaced by the Study ID). All subsequent data handling was done using Study ID. In this way, if a circumstance arose that required the identity of the neonate to be revealed to the clinical/management team, the primary researcher would be able to link Study ID to the original identifier and identify the individual to whom the sample or information related to. This was not required during the conduct of the study.

Due to both the specific nature of the population under study and the short timeframe involved, it was recognized that some personal data collected in the conduct of this study may be recognizable and able to be traced back to the included neonates. As personal demographic data, such as gender, weight and age at surgery, were essential data points for the study it was therefore decided that there would be non-disclosure of the time period during which the study took place in order to minimize any breach of patient confidentiality.

4.4.8.4 Data management

Paper-based data extraction sheets, labelled by Study ID, were used for the secondary data collection within all clinical areas. These were patient specific and covered the duration of inpatient stay or defined period of follow-up. Once collected, the data were then transcribed and imported into Microsoft Excel to facilitate further analysis.

4.4.8.5 Data storage

Manual records containing personal information (date of birth, date of operation etc.) were kept in a locked cabinet within shared locked offices on site at the study hospital, in line with existing Information Governance standards.

Identifiable patient data were stored electronically on the network at the study hospital. Agreement for the temporary storage of non-identifiable electronic data (for data analysis

purposes only) on the UCLan university network was granted as part of the UCLan ethics approval process, but was not required.

All systems in use were user-specific and password protected, therefore all data files were individually password protected. Any de-identified data transferred out of the study hospital for the purposes of research meetings or supervision was done so in line with existing Information Governance policy and procedures.

Following thesis submission, all data will be stored in the Trust until minimum storage requirements have been met. Following this, it will be destroyed along with any additional data collected as part of departmental audit as per Trust guidelines.

4.5 Findings

4.5.1 Summary of group characteristics

During the 4-month data collection period, 25 neonates underwent congenital cardiac surgery at the study hospital. Of these, three neonates were excluded due to prematurity; one neonate was excluded due to previous non-cardiac surgery and one having had preoperative diagnosis and treatment of necrotising enterocolitis. One neonate initially recruited was excluded as cardiac surgery was not via a midline sternotomy approach (N5). Consequently, 19 neonates were included in the study, 15 of whom were male. Summary characteristics of the included neonates can be viewed in Table 4.1.

Seven neonates (N3, N4, N9, N14, N17, N18 and N20) were classified with cardiac lesions having two complete ventricles with no aortic arch obstruction. A further six neonates (N1, N9, N11, N12, N13 and N19) were classified with two complete ventricles and aortic arch obstruction. Three neonates (N2, N6, and N8) had a univentricular heart without aortic outflow tract obstruction; whilst the remaining three neonates (N7, N15 and N16) had a univentricular heart with aortic arch obstruction (also termed hypoplastic left heart syndrome, HLHS). Two of the neonates (10.5%) had genetic syndromes (N1, N8).

Table 4.1: Summary data matrix of neonatal characteristics (ordered by feeding pattern: minimal interruption; moderate interruption; severe interruption; no feeding)

Neonate	WAZ category at birth	Preoperative location	Prostaglandin infusion	Preoperative MSSA status	Preoperative length of stay	Preoperative feed volume	Type of feed	Kcal/kg/d	Protein/kg/d	Fat/kg/d	CHO/kg/d	WAZ category at surgery	Age at surgery (d)	Diagnosis category	Operative risk category	Highest serum lactate (ICU)[+]	Postoperative RRT	Days when feed disprupted	Length of postop stay (d)	WAZ category at end of follow-up	Mode of feeding at discharge*	Diuretics at discharge	PNI (Onodera)[$]	Infection complication
3	2	Ward	N	-ve	15	140	Aptamil	93	1.8	4.8	10.2	2	15	1	2	3.3	N	2	21	2	Breast	N	51	N
4	2	Ward	Y	TNP	10	120	Aptamil/ EBM	77	1.7	4.2	8	2	10	1	2	4.1	Y	2	8	2	Breast/bottle	N	51	Y
6	2	Ward	Y	-ve	25	120	Infantrini	121	3.1	6.5	12.4	2	25	3	3	2.0	N	2	8	1	Bottle	Y	72	N
9	2	Ward	Y	+ve	11	120	EBM	95	1.8	5.9	9.9	2	18	1	2	4.0	N	4	14	2	Bottle	Y	36	N
11	2	ICU	Y	-ve	7	70	EBM	47	0.9	2.9	4.9	2	21	2	3	2.8	N	2	8	2	Bottle	Y	51	N
12	2	Ward	Y	-ve	8	135	EBM	91	1.8	5.7	9.4	2	9	2	1	2.4	N	1	7	2	Bottle	Y	TNP	N
14	2	Ward	Y	TNP	10	155	EBM	105	2	6.5	10.8	2	12	1	2	3.8	N	2	8	2	Breast	Y	66	N
17	2	ICU	N	-ve	2	115	C&G	76	1.5	3.9	8.4	2	8	1	3	2.4	N	2	6	2	Bottle	Y	50	N
18	1	Ward	Y	-ve	26	135	Infantini	136	3.5	7.3	13.9	1	27	1	4	2.1	N	3	10	1	Bottle	N	TNP	N
20	NR	ICU	N	TNP	1	75	Atamil	50	1	2.6	5.5	1	22	1	3	2.2	N	3	8	1	Bottle	Y	41	Y
15	2	Ward	Y	-ve	14	125	EBM	84	1.6	4.5	9.1	2	14	4	4	14.6	Y	4	62	2	PEG	NA	64	Y
16	2	Ward	Y	-ve	2	90	SMA	60	1.1	3.3	6.8	2	7	4	4	12.8	Y	4	72	1	PEG	NA	56	Y
19	2	ICU	Y	TNP	4	26	EBM	18	0.4	0.7	1.8	1	13	2	3	6.0	Y	8	41	1	Bottle	N	41	Y
1	2	Ward	Y	-ve	5	150	Aptamil	99	1.9	5.1	10.9	2	10	2	3	2.6	Y	6	21	1	Bottle	Y	TNP	N
8	2	Ward	Y	-ve	2	120	C&G	79	1.6	4.1	8.8	1	19	3	3	3.0	N	6	30	1	Bottle	Y	51	Y
10	2	Ward	Y	-ve	5	150	EBM	100	2	6.3	10.5	2	11	2	3	2.9	Y	14	65	2	NGT	N	61	Y
13	2	ICU	Y	TNP	5	105	SMA	70	1.3	3.8	7.9	2	24	2	2	2.9	Y	21	72[†]	1	NGT[†]	NA	32	Y
2	1	ICU	Y	-ve	5	80	EBM/ Similac	53	1.1	3	5.6	2	18	3	4	9.6	Y	15	15[†]	NA	None[†]	NA	54	N
7	2	ICU	Y	TNP	16	86	EBM	58	1.1	3.6	6	1	19	4	4	6.5	Y	32	32[†]	NA	None[†]	NA	70	Y

WAZ = weight-for-age z-score (1 = underweight, 2 = normal weight); MSSA = Methicillin-sensitive Staphylococcus aureus; ICU = intensive care unit; RRT = renal replacement therapy; RRT = renal replacement therapy; PNI = prognostic nutritional index; TNP = test not performed; NA = not applicable; NGT = nasogastric tube; PEG = gastrostomy tube; *definitive feeding outcome at hospital discharge/death (may be later than 42 days); [†] Death; ** High energy formula; NR = not recorded; [$] to nearest whole number; [+] to nearest decimal place

Prostaglandin had been administered preoperatively to the majority of neonates (84%) for a median length of treatment of 9 days (IQR 5, 14 days) - those neonates not receiving prostaglandin were N3, N17, and N19. All neonates received full or partial enteral feeds prior to surgery. For those neonates spending their preoperative stay on the cardiac ward, two (10%) were exclusively orally fed (N8, N16), with 7 receiving oral feeds with nasogastric tube supplementation (N1, N4, N6, N10, N12, N14, N18). The remaining three neonates on the ward pre-operatively were fed exclusively via nasogastric tube (N3, N9, N15), as were all preoperative neonates on intensive care (N2, N7, N11, N13, N17, N19 and N20). Feeding volumes were greater than 120ml/kg in ten of the included neonates.

Mean age at the time of surgery was 15.9 days (SD 6.1 days) with mean weight of 3.28 kg (SD 0.4 kg). All neonates underwent surgery under cardiopulmonary bypass with a median duration of 2.6 hours (IQR, 2.3, 3.3 hours). In addition, 17 (89%) underwent circulatory arrest, with 10 (59%) of these cooled to body temperatures less than 28 degrees. Mean duration of circulatory arrest was 112 minutes (± 57 minutes), with a mean cross clamp time of 27 minutes (± 7minutes).

ECMO was needed for two neonates, one due to failure to wean from CPB following intraoperative revision of the initial procedure (N15), and in one infant with postoperative fulminant sepsis (N7). One further neonate (N20) required intraoperative revision, and one (N13) required postoperative reoperation for further tightening of a pulmonary artery band. Postoperative cardiac catheterization was required in 2 infants, one for diagnostic reasons (N13) and one to create an atrial septal defect which was abandoned due to patient deterioration (N2).

Two neonates (10.5%) were born large for gestational age (N10, N14) but with normal WAZ scores. Only one neonate was born small for gestational age (N18), also having an underweight WAZ score both at the time of surgery and hospital discharge. One further neonate was in an underweight WAZ category at birth, although born at an appropriate size for gestational age, but by the time of surgery had achieved a normal WAZ score although subsequently died during follow up (N2). Three further neonates (N7, N8, and N19) all born in a normal WAZ category had crossed below –2 SDS (i.e. from 50^{th} to below the 2^{nd} centile line) and fallen into an underweight WAZ category by the time of surgery. One of these neonates (N7) died during follow-up, and the remaining two were unable to regain normal WAZ category status by the time of discharge. By the time of hospital discharge or follow-up, a further four babies were classified in an underweight WAZ category having failed to thrive during hospitalization (N1, N6, N13, N16). For the 16 neonates who were able to have Onodera's prognostic nutritional index calculated from preoperative blood tests, median values were 50.9 (IQR 47.8, 61.8).

One neonate (N20) went for emergency cardiac surgery from the intensive care within 24-hours of arrival at the study hospital. One neonate (N2) had emergency surgery following a failed medical interventional cardiac catheterisation procedure with cardiac arrest, having been an inpatient preoperatively on the cardiac ward. Three further neonates (N7, N11, and N17) were admitted to intensive care pre-operatively and went to cardiac theatre during the same ICU admission. For neonates waiting for surgery on the cardiac ward the median pre-operative length of stay was 10 days (IQR 9.75 days), whereas for those neonates who went to surgery already an inpatient on intensive care, the median length of preoperative stay was 5 days (IQR 2, 7).

All neonates were MRSA negative. A preoperative Staphylococcus aureus status could be determined in 13 of the neonates who had preoperative MSSA surveillance screening in accordance with the current cardiac surgical care bundle. This resulted in a carriage rate of 8% (n=1). This neonate was subsequently decolonised prior to surgery as per guidelines. The six neonates who were not screened gave a care bundle non-compliance rate of 32%.

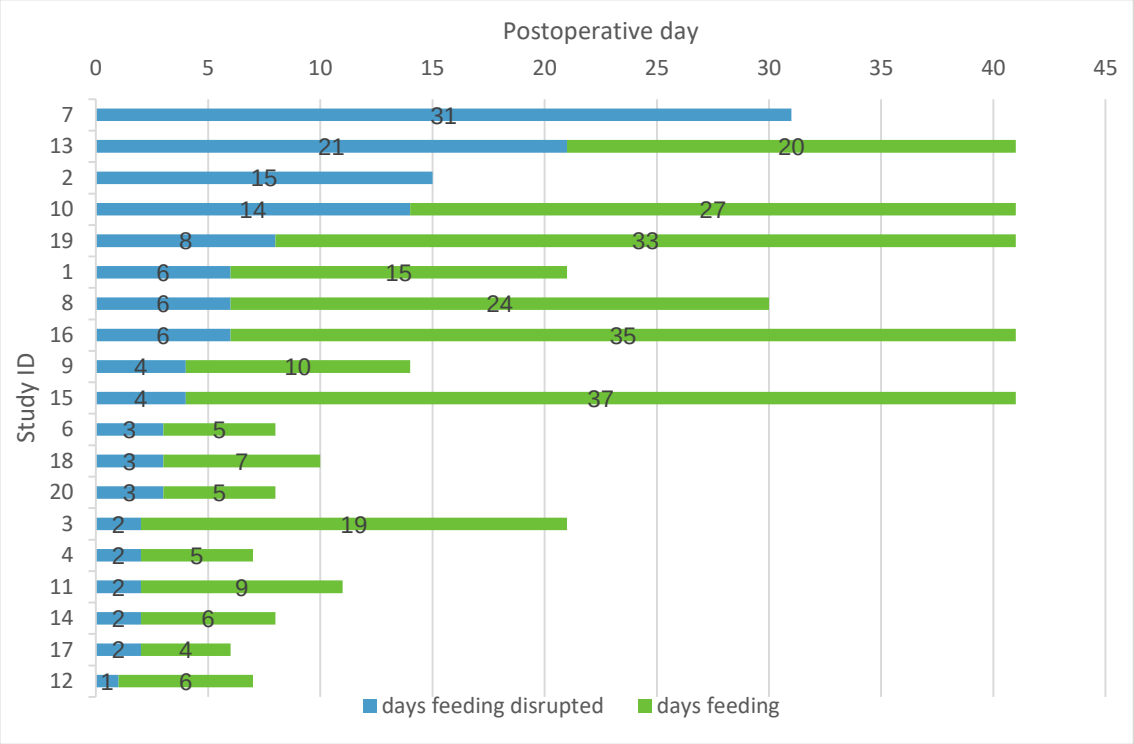
Predictably, the highest operative risk category (greater than 10%) included all neonates with diagnosis category 4 (a univentricular heart lesion with aortic arch obstruction i.e. HLHS). In addition, the neonate (N2) requiring emergency surgery following failed cardiac catheterisation and preoperative cardiac arrest was also included in this category. Four neonates (N1, N6, N8, N10) had a predicted surgical risk between 3 - 10%, with the most common risk category (36.8%) being between 1 - 3% for seven neonates (N3, N4, N9, N11, N12, N13, N19). The remaining four neonates (N14, N17, N18 and N20) all had operative risks below 1%.

Following initiation, enteral feeds were disrupted on 135 out of 382 days of follow up (35%), with the majority of disruptions occurring on intensive care (95%). For those neonates who were enterally fed, time to first feed (in hours) ranged from the earliest at 5 hours after ICU admission, to a maximum of 87 hours. Median hours to first feed was 18hr (IQR 14, 32).

As can be seen from Figure 4.1 two neonates (N2, N7) did not receive enteral feeds at any time during the postoperative period, with both dying on the intensive care unit on postoperative day 15 and 31 respectively. In addition, four further neonates (N10, N13, N15, and N16) remained inpatients at the time of completion of follow-up, with one being discharged on the last day of data collection (N19). All 13 neonates discharged home before the end of follow-up were fully feeding orally, with two (N3, N14) fully breastfeeding and one (N4) feeding via both breast and bottle. The remaining neonates were all feeding via bottle (N1, N6, N8, N9, N11,

N12, N17, N18, N19, and N20). Median length of postoperative stays for these neonates discharged home were 7 days (IQR 8, 21).

Figure 4.1: Days when enteral feeding was disrupted versus days of no disruption (ordered by days of disruption)



With respect to the four neonates who remained inpatients at the end of the data collection period, two (N15, N16) went on to have insertion of gastrostomy tubes prior to discharge home, one was discharged home with a nasogastric tube in situ but taking some oral feeds (N10), and one remained nasogastric tube fed and later died on the cardiology ward 10 weeks post-surgery (N13).

4.5.2 Neonatal chronologies

The complete chronology for each included neonate can be found in Appendix 15. A synopsis of the chronology is provided in the following sections which describe the enteral feeding interruption categories devised to illustrate the pattern of enteral feeding for each neonate, and to reflect the enteral feeding trajectory identified within the chronology. The process of categorisation was not always clear cut, and not always dependent on endpoints of feeding achievement such as weight gain. Rather, a more critical, intuitive interpretation was applied, with the aim to clarify and represent collective feeding experiences using descriptive rather than measurable markers of growth or nutritional achievement, to better identify the barriers to feeding which the neonates faced, and the overall impact of these on feeding progression and ultimate postoperative feeding success.

4.5.2.1. Neonates with minimally interrupted enteral feeding

Neonates in the minimally interrupted category were characterized as having early enteral feed initiation (typically within 24 hours of surgery) but experienced frequent feed disruption for procedural reasons which occurred within the context of a relatively short postoperative ICU length of stay. Following transfer to the cardiac ward no further feeding disruption occurred and there was quick progression to full enteral feeding.

There were ten neonates categorised as achieving minimally interrupted enteral feeding during their postoperative stay. A tabulated summary of key characteristics can be viewed in Table 4.2. Nine neonates (N4, N6, N9, N11, N12, N14, N17, N18 and N20) experienced a similar postoperative course to the time of hospital discharge, with all spending less than one week in the intensive care unit prior to a stay on the cardiac ward less than or equal to one week prior to discharge home fully orally feeding. The remaining neonate (N3) experienced a similar postoperative course on the intensive care unit but had a longer ward length of stay following ICU discharge on postoperative day 3.

Five of the neonates (N3, N4, N6, N9 and N12) were antenatal diagnoses and had been commenced on prostaglandin infusion immediately after birth, with all but one being transferred directly to the cardiac ward whilst awaiting surgery. One neonate (N9) had required intubation and mechanical ventilation at the local neonatal unit for prostaglandin related apnoea, therefore had initially been admitted to the intensive care unit prior to stabilisation, subsequent extubation and transfer to the cardiac ward to await surgery. All four of these neonates were enterally fed at a minimum volume of 120ml/kg/day whilst waiting for surgery.

The remaining five neonates (N11, N14, N17, N18 and N20) were postnatal diagnoses, and all were admitted to the intensive care unit following some degree of cardiovascular collapse/compromise at the time of presentation. Two of the neonates (N14, N18) were stabilised and subsequently transferred to the cardiac ward to await surgery, with both achieving an enteral intake prior to their operation of more than 120ml/kg/day. For the remaining three neonates who remained on intensive care (N11, N17, and N20) none managed to achieve this degree of enteral feed volume; however, all managed the minimum ICU feed requirement of 55kcal/kg/day determined by Teixeira-Cintra et al (2011) prior to ICU discharge. Onodera's Prognostic Nutritional Index ranged from 35 (N9) to 71 (N6); two neonates did not have a preoperative serum albumin level performed to enable calculation. Median group values for Onodera's PNI were 50.8 (IQR 47.8, 54.8).

Table 4.2: Characteristics of neonates with minimally interrupted enteral feeding

Neonate	Diagnostic category	Age at surgery (days)	WAZ at operation	Preoperative location	Preoperative feed volume (ml/kg/day)	Method of preop feeding	Preoperative MSSA status	Operative risk category	POD of sternal closure	Inotrope score category	PICU mortality risk (%)[+]	Highest lactate[+]	Hours to first feed	Feed disruption days	POD of extubation	Days to full feeds (150)	Early complication	Late complication	Total days of antibiotics[$]	Postoperative days on PICU	Total postoperative LOS	Method of feeding at discharge	Diuretics at discharge	WAZ at discharge
3	1	15	2	Ward	140	Oral/ NGT	-ve	2	1	2	2.3	3.3	8	2	2	6	AKI	Wound dehiscence	2	4	21	Breast	N	2
4	1	10	2	Ward	120	Oral	TNP	2	0	4	2.9	4.1	27	2	3	6	None	Stitch abscess	1	5	8	Breast/ bottle	N	2
6	3	25	2	Ward	120	Oral/ NGT	-ve	3	2	5	1.7	2.0	14	2	4	7	None	None	3	6	8	Bottle	Y	1
9	1	18	2	Ward	120	NGT	+ve	2	4	5	2.2	4.0	17	4	6	9	None	None	5	8	14	Bottle	Y	2
11	2	21	2	ICU	70	NGT	-ve	3	2	3	5.0	2.8	5	2	4	7	None	None	3	6	8	Bottle	Y	2
12	2	9	2	Ward	135	Oral/ NGT	-ve	1	0	2	3.4	2.4	19	1	2	6	None	None	1	4	7	Bottle	Y	2
14	1	12	2	Ward	155	Oral/ NGT	TNP	2	1	1	1.8	3.8	18	2	4	6	None	None	2	5	8	Breast	Y	2
17	1	8	2	ICU	115	Oral/ NGT	-ve	3	0	2	17.6	2.4	15	2	3	6	None	None	1	4	6	Bottle	Y	2
18	1	27	1	Ward	135*	Oral/ NGT	-ve	4	2	4	2.8	2.1	21	3	5	7	None	None	3	7	10	Bottle	N	1
20	1	22	1	ICU	75	Oral	TNP	3	0	1	7.4	2.2	8	3	3	6	None	Wound infection	1	5	8	Bottle	Y	1

WAZ = weight-for-age z-score (1 = underweight, 2 = normal weight); POD = postoperative day; PICU = paediatric intensive care unit; LOS = length of stay; NGT= nasogastric tube; TNP = test not performed; AKI = acute kidney injury; * = high energy formula; [+]to nearest decimal place; [$]during initial hospital admission; -ve = negative, +ve = positive

In keeping with the nature of most neonatal surgery all neonates bar two (N3, N18) were in a medium surgical risk category, with N3 in a low risk category and N18 in a high-risk category. Immediately after surgery, all neonates experienced bleeding at or more than 20ml/kg in the first 24hr, with only one neonate (N15) meeting the threshold for major bleeding. Four of the ten neonates (N4, N12, N17, and N20) underwent primary sternal closure at the end of the operation. Of the six who underwent delayed sternal closure on the intensive care unit, this occurred for one (N3) on postoperative day 1, for three (N6, N11, N18) on postoperative day 2, and for two neonates on postoperative day 4 (N9, N14).

Serum lactates were at their highest value for all neonates on the day of surgery, settling to within normal values within 28 hours which allowed enteral feeds to be commenced. Highest lactate observed in this group was 4.07. Mean duration to first feed was 15.2 hours (± 6.7 hr.). Total fluid intake on the day of surgery was significantly greater than the 25ml/kg/day guideline for all neonates and ranged from 54 (N3) to 252 (N6) ml/kg/day, primarily dependent on the extent of postoperative bleeding. Despite this large volume load, neonates managed to achieve a cumulative fluid balance less than 5% positive by PICU day 2 (postoperative day 1), with the majority in a negative balance with no evidence of acute renal injury. One neonate (N4) received peritoneal dialysis for management of fluid balance for a period less than 24-hours.

Once feeds had been commenced there were numerous subsequent feeding disruptions for procedural reasons, typically delayed sternal closure, extubation, and drain removal. Following transfer to the ward, no further feed disruptions occurred. Days on which feeding was disrupted accounted for between 10% and 38% of their total hospital stay.

All neonates were extubated on or by postoperative day 6, with eight of ten neonates extubated on or before postoperative day 4 (N3, N4, N6, N11, N12, N14, N17 and N20). All bar one neonate (N11) were discharged from intensive care within 24hrs of extubation, with two neonates being transferred later the same day (N14, N17). All neonates were discharged directly to the cardiac ward, with the longest postoperative intensive care length of stay being seven days for all but one neonate (N9).

Once on the cardiac ward, the longest length of stay was 7 days (N11) for all neonates except N3. This neonate, following transfer to the ward on postoperative day 3, had trouble in progressing from nasogastric to oral feeding, resulting in a longer hospital length of stay than the other neonates in this category. Following confirmation of a safe swallow on postoperative day 11, oral feeds were reintroduced by bottle. Due to sternotomy wound dehiscence on postoperative day 14 she had been started on oral antibiotics, which may have adversely

influenced oral feeding success. Full breast-feeding was established by postoperative day 21 when she was discharged home.

Of the remaining neonates, seven (N4, N6, N12, N14, N17, N18 and N20) were discharged home on or before three days after transfer to the ward, and all by postoperative day 14. All neonates in this category were discharged home orally feeding with over two-thirds remaining on oral diuretics. Two were exclusively breast feeding (N3, N14), one was orally feeding via breast or bottle (N4), and the remaining seven were fully bottle feeding. Seven neonates (N6, N9, N11, N12, N14, N17, and N20) were receiving diuretics at the time of hospital discharge. With respect to postoperative growth velocity, four neonates (N3, N4, N6, and N9) had demonstrated postoperative weight gain, with the remaining six having lost weight at the time of hospital discharge. The median value for postoperative growth velocity was - 5.1 (IQR -14.5, 8.4) for the nine neonates with similar length of stays (excluding N3 for the atypical length of stay previously identified). However, despite the overall observed weight-loss, only one neonate (N6) crossed one standard deviation in weight-for-age *z*-score and fell into an underweight category. This growth failure had been identified by the ward dietician and feeds had been changed to a high-energy formula, with a plan for local dietetic review post discharge.

In summary, all neonates had a straight forward initial postoperative recovery, with only one neonate (N3) requiring peritoneal dialysis for a short period of time. The majority experienced no complications, and when complications did occur they were wound related, with one sterile wound dehiscence in the neonate requiring dialysis (N3), a stitch abscess (N4) and superficial surgical site infection (N20). These last two complications occurred after hospital discharge and did not require readmission. All were discharged home having achieved full oral feeding, with a median length of postoperative stay at 8 days (IQR 8, 10.75).

Careful consideration had been required in the categorisation of N3 within this group in view of the extended postoperative ward length of stay, and the difficulties establishing oral feeding. The decision to include her in this group was primarily based on the fact that enteral feedings continued at full volumes via NGT during the time of oral feeding difficulty, and that ultimately some delay may have been due to persisting with bottle feeds rather than allowing breast feeds to be established. Changing category based purely on her longer postoperative length of stay was not felt to accurately represent her enteral feeding trajectory.

In this group, elevated serum lactate in the first 24 hours after surgery was the main reason for delaying the initiation of enteral feeding beyond the goal for introducing feeds as per unit protocol. Subsequent feed disruptions for required clinical procedures were the main reason

preventing feed progression and an inability to achieve minimal ICU feed requirements as advocated by Teixeira-Cintra et al (2011). However, following transfer to the ward, all neonates quickly established full enteral feeding volumes and were orally feeding on hospital discharge.

4.5.2.2 Neonates with moderately interrupted enteral feeding

Neonates in the moderately interrupted category were characterised as having longer lengths of intensive care stay than those neonates in the minimally interrupted category, with greater delay before enteral feeds were initiated. Early cardiovascular complications with high inotropic requirements were a feature for all neonates, and all exhibited some degree of feeding intolerance. A summary of the neonates in this category is presented in Table 4.3.

Three neonates (N15, N16 and N19) were identified within this category. Two of them (N15, N16) were antenatal diagnoses of congenital heart disease. All three were born an adequate size for gestational age and within a normal WAZ category. The two neonates with an antenatal diagnosis had been cared for on the cardiac ward prior to surgery, with differing preoperative length of stays, but all neonates were between one and two weeks of age at the time of surgery. All had been enterally fed to some degree – the one neonate on intensive care prior to surgery (N19) achieving the lowest volume at 26ml/kg/day, as compared to N15 who achieved the maximum intake of 125ml/kg/day. Median values for preoperative Onodera's PNI were 56.1 (IQR 48.5, 60.2) in this group.

Neonates 15 and 16 were both in the same diagnostic category and on a univentricular surgical pathway, having undergone high-risk surgery. An additional intraoperative diagnosis of a descending aorta to pulmonary artery fistula was made in N15 when the baby failed to separate from cardiopulmonary bypass at the end of the operation, at which time the baby was transitioned to extracorporeal membrane oxygenation (ECMO) in the operating theatre and transferred to the intensive care unit until an interventional procedure could be performed in the cardiac catheterization laboratory on postoperative day 2.

High levels of postoperative cardiovascular support were a feature in all three neonates; in addition to the neonate requiring ECMO, the remaining two neonates were in the maximum vasoactive inotrope score category. Elevated serum lactate levels and early postoperative complications subsequently delayed the initiation of enteral feeds in all three neonates, with a median time to feed initiation of 55 hours (IQR 43.5, 71), and peak serum lactate concentration in this group reaching a median level of 12.8 (IQR 9.4, 13.7). Parenteral nutrition was started in two of the neonates (N15, N16) on postoperative day 1 and 2 respectively. In the remaining neonate (N19), feeds were withheld four days following initial re-introduction

Table 4.3: Characteristics of neonates with moderately interrupted enteral feeding

Neonate	Diagnostic category	Age at surgery (days)	WAZ at operation	Preoperative location	Preoperative feed volume (ml/kg/day)	Method of preop feeding	Operative risk category	POD of sternal closure	Inotrope score category	PICU mortality risk (%)[+]	Highest lactate (mmol/L)[+]	Hours to first feed	Feed disruption days	POD of extubation	Days to full feeds (150)	Early complication	Late complication	Postoperative days on ICU	Total days of antibiotics[$]	Total postoperative LOS (d)	Method of feeding at discharge*	Diuretics at discharge	WAZ at discharge
15	4	14	2	Ward	125	NGT	4	8	5	ECMO	14.6	87	4	16	15	ECMO; major bleeding; AKI; new onset seizures; mediastinitis	Unsafe swallow	19	49	62	GT	Y	2
16	4	7	2	Ward	90	Oral	4	3	5	4.0	12.8	55	4	11	14	IVH; AKI; suspected sepsis; reintubation; left phrenic nerve palsy requiring operation	Wound infection; unsafe swallow	14	23	72	GT	Y	2
19	2	13	1	ICU	26	Oral	3	2	5	14.6	6.0	32	8	12	12	Malignant arrhythmia; LCOS; AKI; wound dehiscence (suspected infection)	ICU readmission; CLaBSI; new onset seizures	23	27	41	Bottle	N	1

WAZ = weight-for-age z-score (1 = underweight, 2 = normal weight); ICU = intensive care unit; POD = postoperative day; LOS = length of stay; ECMO = extracorporeal membrane oxygenation; AKI = acute kidney injury; IVH = intraventricular haemorrhage; ICU = intensive care unit; LCOS = low cardiac output state; CLaBSI = central line associated bloodstream infection; [+]to nearest decimal place; NGT = nasogastric tube; GT = gastrostomy tube; [$]during initial hospital admission; *definitive feeding outcome at hospital discharge/death (may be later than 42 days)

due to acute clinical deterioration with intractable dysrhythmia, and a resulting low cardiac output state with rising serum lactate.

All three neonates experienced multiple early complications after surgery spending two or more weeks on intensive care after surgery. One neonate (N15) required early chest re-exploration whilst on ECMO to control major bleeding, a known complication due to the need for anticoagulation of the extracorporeal circuit. All neonates required some form of renal replacement therapy for fluid overload and/or acute kidney dysfunction, either in the form of continuous venovenous haemofiltration (N15) or peritoneal dialysis (N16, N19). The minimum amount of non-nutritive fluid administration was observed at 7ml/kg/hr (N19), with a maximum of 35ml/kg/hr observed in the neonate with surgical bleeding on ECMO support (N15), the majority of which was as blood transfusion. Two neonates (N16, N19) managed to achieve a negative cumulative fluid balance by 48hr after surgery.

Late complications were also a feature of this category, which also extended post-ICU length of stay. One neonate (N19) required ICU readmission 48 hours after initial discharge due instability in controlling his existing postoperative dysrhythmia (N19), and spent an additional 9 days on the intensive care unit. Two neonates (N15, N16) remained inpatients on the cardiac ward six weeks after surgery, when active follow-up was discontinued, both having failed to feed orally and awaiting gastrostomy tube insertion for long term feeding management. The remaining neonate (N19) was discharged home on day 42 fully bottle feeding with diuretics discontinued.

All neonates experienced an infection-related complication along with other system complications, and all required antibiotic therapy for more than a third of their total postoperative length of stay. One neonate (N15) with late delayed sternal closure on postoperative day 8 was treated for mediastinitis; one (N16) had suspected sepsis on intensive care and later required treatment for deep surgical site infection, with the remaining neonate experiencing surgical site infection with wound dehiscence and later bloodstream infection.

One neonate (N15) remained in a normal weight category for the duration of his hospital stay, whereas neonate N19 dropped into an underweight WAZ category by the time of surgery and remained there at the time of hospital discharge. The remaining neonate (N16) having been in a normal WAZ category both at birth and time of operation, had dropped into an underweight WAZ category by the time of cessation of follow up 6 weeks after surgery. Despite the duration of both intensive care and ward length of stay, the percentage of days on which feeds were disrupted were generally lower than in comparison to the neonates in the minimally interrupted feeding category, although absolute numbers were greater.

The key barrier to feeding in this group was the significant delay before initiating enteral feeds due to high serum lactate levels. Two of these three neonates were in the highest surgical risk category, and this was reflected in the highest postoperative lactates seen within the cohort. Additionally, the presence of feeding related complications – feed intolerance and/or inadequate swallow – further delayed feed progression. For all neonates in this category, it took two weeks before these neonates achieved full enteral feeding requirements. In addition, incidence of failure to feed orally after surgery was high with two of the three neonates (N15 and N16) requiring gastrostomy tube insertion and all neonates experienced significant infection complications in association with other forms of postoperative morbidity.

4.5.2.3 Neonates with severely interrupted enteral feeding

Neonates experiencing severely interrupted enteral feeding were less homogenous than the other feeding categories but generally existed within the context of late postoperative complications, either with or without an extended length of ICU stay. These complications had a profound impact on enteral feeding progression. The timing of feed initiation was variable, incorporating both the shortest and longest durations seen across the whole cohort. A unifying characteristic, however, was that following commencement of enteral feeds there were numerous days when feeding was disrupted which resulted in sub-optimal enteral feeding and a long duration before full enteral feeding could be established. The characteristics of these neonates can be viewed in Table 4.4.

Four neonates (N1, N8, N10, and N13) were in this category. All neonates experienced significant delay (>14 days) before achieving full enteral feed volumes of 150ml/kg/day, all related to the presence of postoperative complications of varying aetiology. Three of the four neonates were in a medium surgical risk category, with one (N13) in a low risk. Two neonates (N1, N8) were the only ones in the cohort noted to have chromosomal abnormality. The neonates within this group fell equally into two similar but distinct patterns – either an initial uncomplicated intensive care stay with late deterioration; or a long, complicated intensive care stay for the duration of follow-up. Incidence of postoperative complications was also high in this subset, with a high proportion of infective complications which resulted in a high percentage of days when antibiotic therapy was administered.

Neonates in this category experienced length of postoperative intensive care stays greater than 10 days except for N1, whose initial intensive care progress and length of stay began similarly to neonates in the minimally interrupted enteral feeding category, albeit with a more prolonged time to first enteral feed (70 hours). However, following transfer to the cardiac ward having achieved enteral feeding volumes of 60ml/kg/day, this neonate was suspected to

Table 4.4: Characteristics of neonates with severely interrupted enteral feeding

Neonate	Diagnostic category	Age at surgery (days)	WAZ category at operation	Preoperative location	Preoperative feed volume (ml/kg/day)	Method of preop feeding	Operative risk category	% mortality risk on ICU admission (PIM2)[+]	POD of sternal closure	Hours to first feed	Feed disruption days	Days to full enteral feeds	Early complication	Late complication	Total days of antibiotics[$]	Postoperative days on ICU	Total postoperative LOS	Method of feeding at discharge*
1	2	10	2	Ward	150	Oral/ NGT	3	1.8	0	70	6	21	None	NEC (Bell's Stage Ia)	14	6	21	Bottle
8	3	19	1	Ward	120	Oral	3	1.2	0	15	6	22	None	ICU readmission; CLaBSI; suspected meningitis	27	11	30	Bottle
10	2	11	2	Ward	150	Oral/ NGT	3	2.7	3	33	14	16	Reintubation (x 2); LRTI; VAP; left phrenic nerve palsy requiring operation; sepsis	NA	19	42	65	NGT
13	2	24	2	Ward	105	NGT	2	1.2	5	5	21	38	Reintubation; NEC (Bell's Stage Ia); VAP; cardiac reoperation	NA	17	64	72	NGT[†]

WAZ = weight-for-age z-score (1 = underweight, 2 = normal weight); POD = postoperative day; ICU = intensive care unit; LOS = length of stay; CLaBSI = central line associated blood stream infection; LRTI = lower respiratory tract infection; VAP = ventilator associated pneumonia; NEC = necrotising enterocolitis; VAP = ventilator associated pneumonia; [+]to nearest decimal place; NGT = naso-gastric tube; [†]late death; [$]during initial hospital admission; *definitive feeding outcome at hospital discharge/death (may be later than 42 days); NA = not applicable (remained on ICU at end of follow-up)

have necrotizing enterocolitis which led to all enteral feeds being withheld as part of medical management. Exclusive parenteral nutrition was administered for a total period of five days before feeds were re-introduced, therefore there was a three-week delay from time of surgery before full enteral feeding was able to be established at 150ml/kg/day. Although WAZ at birth and time of surgery had been normal, by the time of hospital discharge this neonate had dropped into an underweight WAZ category.

N8 was a postnatal diagnosis born at normal weight and fully fed via bottle at 120ml/kg/day, with an Onodera's PNI calculated at 50.6. Although born in a normal WAZ category, by the time of surgery he had dropped into an underweight WAZ category. Surgery was in a moderate risk category, and maximum VIS score on the day of admission correlated with this. Enteral feeds were started 15 hours following ICU admission when serum lactate had normalized, and again, this neonate experienced an initial intensive care stay comparable to neonates in the minimally interrupted category - extubated on postoperative day 2 onto non-invasive respiratory support with minimal oxygen requirements, two feed disruptions for a transient elevation in serum lactate and extubation, transfer to the high dependency unit on postoperative day 4 due to ongoing CPAP requirements, receiving 80ml/kg/day of enteral feeds via nasogastric tube.

However, on postoperative day 9 feeding was disrupted due to acute deterioration with oxygen desaturation episodes and bradycardia due to sepsis, requiring intensive care readmission for reintubation and antibiotics. At the time of readmission, body weight had decreased by 210g since surgery, despite achieving a feeding volume of 120ml/kg/day whilst on HDU. After successful extubation on postoperative day 12, transfer to the cardiac ward occurred two days later, at which time feeds had reached 93 ml/kg/day. However, following two ICU admissions his lowest recorded weight was on postoperative day 15, and 380g below operative weight. A weight increase was noted prior to discharge home on postoperative day 30, at which time this baby was fully bottle feeding with an intake of 135ml/kg/day. WAZ at discharge remained in an underweight category and cumulative weight gain throughout the inpatient stay was 100g.

For the remaining two neonates in this group (N10 and N13) both remained inpatients on the intensive care unit six weeks after primary operation/cessation of active follow-up. Both required further surgical intervention (diaphragm plication and cardiac reoperation respectively). Frequent feed disruptions for investigation and subsequent treatment of ongoing ventilator dependence, in addition to observed feed intolerance demonstrated by high gastric residual volumes, compromised the ability to progress enteral feeds and lead to a significant delay in establishing full feeding volumes.

One of these neonates (N10) was one of only two babies in the study born large for gestational age, although with a normal WAZ category both at birth and time of surgery. Preoperative feed volumes of 150ml/kg/day had been achieved, offered orally via bottle with nasogastric tube top-up as required. Onodera's PNI was calculated at 61.

Surgical risk category was moderate, with maximum VIS score postoperatively in accordance. Positive fluid balance at 24 hours led to the initiation of peritoneal dialysis on postoperative day one, and enteral feeding commenced 33 hours following ICU admission. Feeding was subsequently disrupted on nine occasions within the first 14 days, during which time he failed to wean from mechanical ventilation. Seven of these episodes were directly related to attempted or actual extubation. Following multiple investigations, a left phrenic nerve palsy was found to be the cause for weaning failure, but surgical treatment – a diaphragm plication – was delayed until postoperative day 32 due to concerns regarding possible infection, and to allow for completion of subsequent antibiotic treatment.

With ventilation slowly weaning but somewhat complicated by sedation withdrawal syndrome, N10 remained ventilator-dependent at cessation of follow-up. Overall body weight decreased by 30g during the period of follow-up, occurring within the first two-weeks from surgery. Observed growth velocity between lowest weight and weight at completion of follow-up was 24g/day, with enteral nutrition volumes at 145ml/kg/day via nasogastric tube. At completion of follow-up he had remained in a normal WAZ category.

The remaining neonate in this category (N13) also had a complicated postoperative course. Diagnosed with intrauterine growth retardation antenatally, size for gestational age at delivery and WAZ were normal. Following neonatal collapse, he was diagnosed with congenital heart disease and transferred to the intensive care unit where he remained on positive pressure ventilation until surgery. Preoperative enteral feeding via nasogastric tube reached 105ml/kg/day, and Onodera's PNI, calculated at 32, and was the lowest of all study participants.

Surgical risk was in category 2, and his operation was performed on day 22 of life. Moderate inotropic therapy was required postoperatively on the day of surgery, and postoperative serum lactates were less than 2mmol/L within 5 hours of ICU admission at which point enteral feeds were started - one of the earliest commencements of enteral feed seen within the entire cohort. However, subsequently there was only one day (postoperative day 9) during the following three weeks when feeding was not disrupted.

By postoperative day 5, however, N13 was demonstrating an increased effort of breathing limiting further weaning of mechanical ventilation. Airway investigations at this time were

normal, therefore a gradual wean in ventilation occurred over the following days and extubation occurred on postoperative day 10. Within a few hours, however, serum lactates had elevated leading to elective reintubation on postoperative day 11. Necrotizing enterocolitis was considered the potential cause for the raised lactate, therefore enteral feeds were discontinued for 7 days as part of conservative management and parenteral nutrition commenced. Trophic feeds at 1ml/hr were subsequently introduced on postoperative day 18, with parenteral nutrition continuing until enteral feeds of 90ml/kg/day were re-established on postoperative day 25.

During this time, ventilation weaning remained problematic. Concerns of possible pulmonary over-circulation were raised due to ongoing cachexia (despite initial postoperative weight gain, there had been a subsequent weight loss of 250g) and increased work of breathing continued to limit further progression. Cardiac catheterization to investigate pulmonary blood flow was agreed, but a ventilator-associated pneumonia delayed this investigation. When performed on postoperative day 31 the pulmonary blood was significantly elevated, therefore N13 was listed for surgical reintervention. This occurred on postoperative day 34, following which there was an uneventful postoperative recovery. Full feeding re-established the following day, and nutritional progress was seen with gradual weight increases observed following a change to high energy milk and feeding volumes at 120ml/kg/day.

Although subsequent progress had been made with ventilation weaning, at completion of follow-up N13 remained ventilator dependent. At this time, a net weight gain of 430g had been achieved over the six-week period, with a postoperative growth velocity from the lowest recorded weight on postoperative day 20 to completion of follow up of was 19g/day. Nonetheless, WAZ had dropped into an underweight category.

All neonates in this category had longer durations of hospital stay, either on intensive care or on the cardiac ward, which were characterised by experiencing postoperative complications which impacted on feeding progression either through frequency of disruption and/or on duration to successfully achieving full enteral feed volumes. Again, similar to the moderately interrupted feeding category, postoperative infections were clustered along with infection related complications, especially in the two neonates (N10, N13) requiring extended durations of mechanical ventilation.

Careful consideration was given to the categorisation of N1, as features of his intensive care stay were similar to those neonates with minimally interrupted feeding patterns, in as far that it was of relatively short duration but characterised by a high percentage of days when enteral feeds were disrupted. However, the main reason to categorise this neonate as severely

interrupted was because of the added burden of feed disruption following transfer to the ward due to a diagnosis of NEC. Although parenteral nutrition was used, it was 18 days before full feeding volumes were able to be established, and despite nutritional support with parenteral nutrition during this period there was marginal in-hospital weight gain demonstrated, and by the time of hospital discharge a drop in WAZ score from normal to an underweight category was observed.

The key barriers to enteral feeding identified in this group were prolonged hospitalisation following postoperative complications of either respiratory or gastrointestinal aetiology, or a requirement for cardiac reoperation. Significant healthcare associated infection – blood stream infection, ventilator associated pneumonia and presumed sepsis – were common in this category and occurred as an additional burden to primary postoperative complications. Therefore, one could postulate that for this group infection complications were the result of prolonged intensive care stay rather than being the primary cause for it, and that prolonged intensive care occurred due to non-infection primary complications. However, investigations required in determining the need for further cardiac-related surgery, and a requirement to be infection-free at the time of it being undertaken, certainly led to a secondary increase in length of stay, as well as significant failure to progress to full enteral feeds due to the high frequency of feed disruptions.

4.5.2.4 Neonates with no enteral feeding

There were two neonates in the cohort (N2, N7) who did not establish postoperative enteral feeding. Both neonates died on the intensive care unit due to complications following surgery. Both neonates were in the highest surgical risk category, with predicted mortality greater than 25%. Characteristics of the neonates with no enteral feeding can be viewed in Table 4.5.

One neonate (N2) had an antenatal diagnosis and following postnatal cardiology assessment, had been managed at his local neonatal unit on a prostaglandin infusion to grow to a minimum of 3kg. Following desaturation and a requirement for intubation, he was transferred to the intensive care unit on day 14 of life, and as body weight had reached 3kg, he was re-discussed and listed for an interventional cardiac catheterization procedure four days later. At this stage, although born in an underweight WAZ category, he had grown sufficiently to achieve normal WAZ status at the time of this procedure. However, on attempting the ductal stenting procedure, there was significant haemodynamic collapse requiring immediate transfer to the operating theatre for an emergency aorto-pulmonary shunt.

Table 4.5: Characteristics of neonates with no postoperative enteral feeding

Neonate	Diagnostic category	Age at surgery (days)	WAZ category at birth	Preoperative location	Preoperative length of stay	Preoperative feed volume (ml/kg/day)	Method of preop feeding	PNI (Onodera)	Operative risk category	WAZ category at operation	PICU mortality risk (%)[+]	Inotrope score category	Highest lactate (mmol/L)	Non-nutritive fluid intake @ 48hr (ml/kg/day)	POD of sternal closure	Early complication	Late complication	Postoperative days on ICU	Total postoperative LOS	Total days of antibiotics
2	3	18	1	ICU	5	80	NGT	54	4	2	5	5	9.6	125	15	CA; LCOS; AKI; refractory hypoxia, tachyarrhythmia	NA	15	¥	10
7	3	19	2	ICU	16	86	NGT	70	4	1	27	5*	9.7	135	31	LCOS; AKI; ECMO; septicaemia	NEC (Bell's Stage IIIb)	31	¥	31

WAZ = weight-for-age z-score (1 = underweight, 2 = normal weight); POD = postoperative day; ICU = intensive care unit; PNI = prognostic nutritional index; CA = cardiac arrest; LCOS = low cardiac output state; AKI = acute kidney injury; *required ECMO (extracorporeal membrane oxygenation); ¥ = ICU death; [+]to nearest decimal place

N7 was admitted to intensive care on day 4 of life following cardiovascular collapse, having presented at his local hospital the day previously with poor feeding, breathlessness and jaundice. On arrival there was evidence of acute kidney injury and hepatic dysfunction with a coagulopathy. Once lactate levels were normalized, enteral feeds were attempted but there were early concerns regarding possible NEC, despite the absence of radiological signs, in addition to ongoing concerns regarding sepsis despite appropriate antibiotic therapy. He was also noted to have an extended-spectrum beta-lactam producing Enterobacter coli in tracheal aspirates, for which an additional preoperative antibiotic course was given. Subsequently, surgery was postponed twice to optimise his condition. He remained an inpatient on ICU for 15 days prior to operation. Consequently, both neonates were in the highest age percentile at the time of operation.

PIM2 scores for both neonates, calculated at time of initial ICU admission, were in the highest of the cohort. Maximum levels of cardiovascular support were required – N2 was in the highest VIS category, with N7 going onto ECMO on postoperative day 2. Both neonates had problems with postoperative bleeding, not reaching the threshold for major bleeding, but requiring significant volumes of fluid administration in the first 24 hours – 160ml/kg/day and 120ml/kg/day respectively. Both neonates required renal replacement therapy by postoperative day 2, and although delayed sternal closure was attempted once in N2 on postoperative day 3, subsequent cardiac arrest led to chest re-opening. In N7 delayed sternal closure was not attempted due to the severity of his condition. Consequently, at the time of death, both neonates had sternums which remained un-approximated.

Serum lactates remained elevated in both neonates for the duration of their ICU admission, with maximum values of 9.6 (N2) and 9.7 (N7). Parenteral nutrition was started on postoperative day 10 (N2) and postoperative day 3 (N7). Earlier administration was permitted in N7 due to the liberalisation of fluid restriction in view of ECMO support. Both neonates experienced persistent cardiorespiratory compromise and low cardiac output states despite maximum levels of intensive care support. N2 was re-discussed and scheduled for balloon atrial septostomy to allow better mixing of oxygenated and deoxygenated blood to treat the refractory hypoxaemia, but suffered a fatal hypoxic bradycardic arrest following transfer to theatre on postoperative day 15, prior to the procedure commencing. N7, after a long and protracted course on ECMO due to fulminant sepsis who underwent high-risk laparotomy on postoperative day 17, and which demonstrated jejunal ischaemia and perforation, failed twice to wean from mechanical support. Treatment was withdrawn on postoperative day 32 when a third attempt to wean from ECMO failed.

The neonates in this feeding category shared preoperative characteristics that identified them as high risk, both on initial ICU admission and with respect to predicted surgical risk. Postoperatively both required high levels of cardiovascular support beyond the first 48 hours of surgery, with persistently elevated serum lactate, and signs of early end-organ dysfunction. In addition, pre-operative feeding was noted to be sub-optimal in both, a characteristic shared with other neonates requiring ICU level of care before surgery. The inability to commence enteral feeding in these babies were persistently elevated serum lactates.

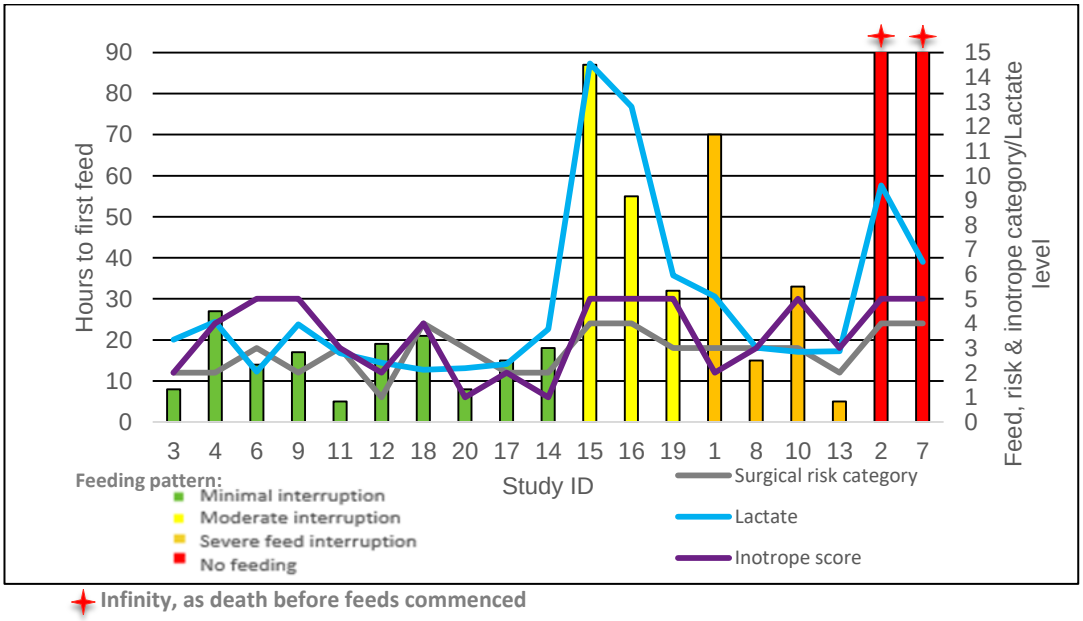
4.5.2.5 Summary of findings regarding categories of feeding

High lactate levels across all feeding categories appeared to have the most influence on whether feed initiation was delayed, as can be seen in Figure 4.2. Although there was a slight increasing trend of delayed feeding with surgical risk category and inotrope score, this trend was not as apparent as there was little difference in risk across feeding categories and all neonates required moderate to high levels of inotropic support or extracorporeal membrane oxygenation (ECMO) postoperatively.

Overall, however, there does appear to be a positive relationship between risk group, inotropic score and lactate at both ends of the categories of feeding pattern spectrum which is not unexpected as sicker neonates will be more cautiously fed; however, this positive relationship does not hold true for all the neonates, and reasons for delaying enteral feed in N10 cannot be explained by this relationship. For this baby it appears inotrope score had the most influence on when enteral feeds were introduced, but it remains unclear why there was such a long delay in comparison to N6 and N9 who had similar inotrope scores and lactate levels but commenced feeds earlier. This variation may be due to the individual practice of the clinician managing care, or alternatively, it may be due to subtle patient characteristics that were not captured through the data collection process. As this baby went on to have a suspicion of necrotizing enterocolitis, his overall enteral feeding pattern was highly disrupted.

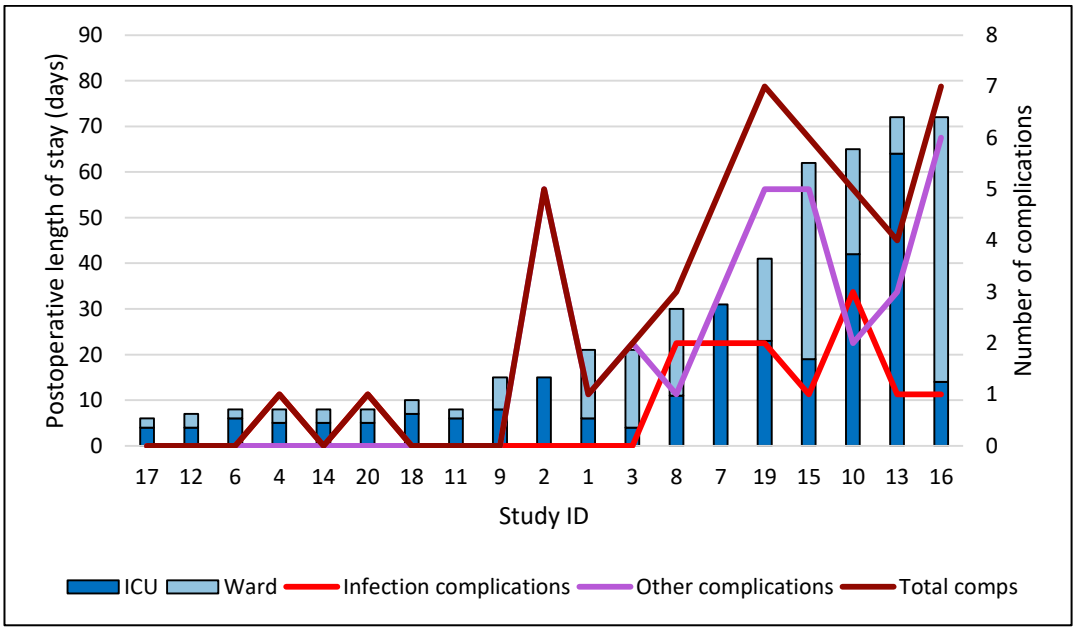
However, timing of feed initiation was not always reflective of eventual feeding interruption pattern, as can be seen in N8 and N13 where, despite early feed initiation, both experienced highly disrupted patterns of postoperative enteral feeding with longer postoperative lengths of stay.

Figure 4.2: Timing of enteral feed initiation and the relationship between surgical risk, inotrope score, enteral feed pattern and serum lactate concentration (ordered by feeding interruption pattern)



With respect to postoperative infection complications, these occurred with greater frequency with increasing feeding interruption pattern, and linearly with increasing length of postoperative stay. If a complication occurred, with the exception of an isolated stitch abscess in N4 and superficial surgical site infection in N20 (both post discharge), there appeared to be an increased risk of further complication, with a clustering effect noted. This is demonstrated in Figure 4.3 where it can be seen that death (in N2 and N7) and increasing length of postoperative stay is associated with multiple complications and an increased risk of postoperative infection.

Figure 4.3: Relationship between complications and postoperative length of stay

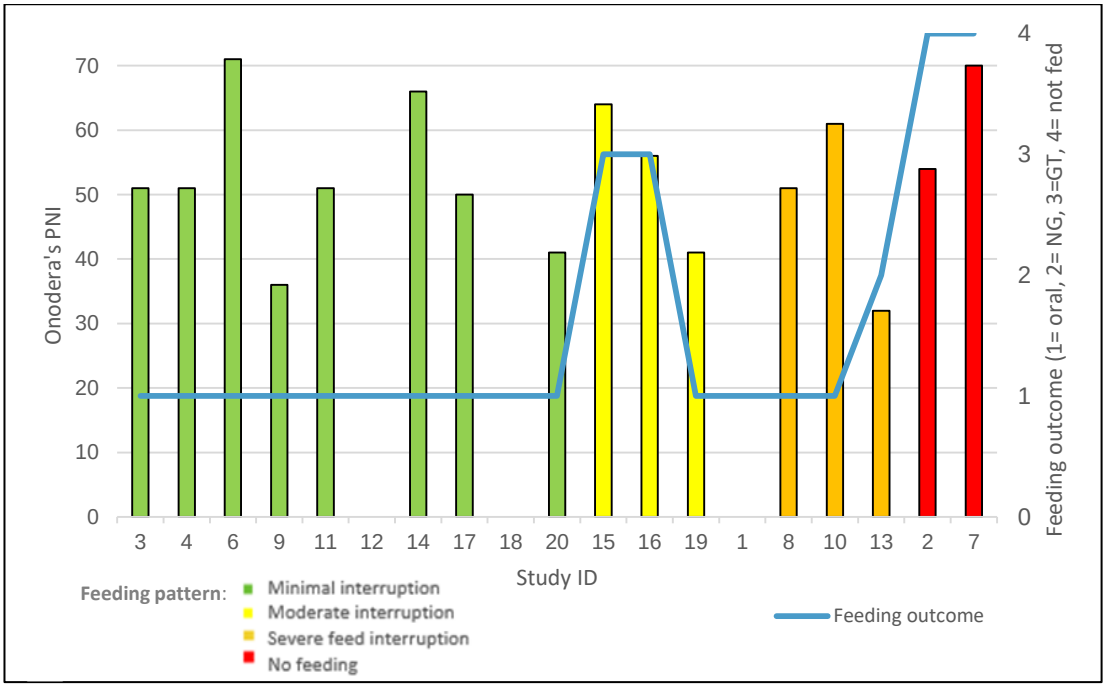


4.5.3 Onodera's prognostic nutritional index (PNI)

Onodera's PNI could be calculated preoperatively for 16 of the 19 included neonates (84%) where preoperative serum albumin levels had been measured. Mean PNI values for the cohort were 52.8 (SD 11.7) with a range from 32 to 71.5. Results did not suggest a relationship between PNI and preoperative feeding achievement, feeding outcome (at discharge or completion of follow-up), or pattern of enteral feeding interruption.

As can be seen in Figure 4.4 showing values of Onodera's PNI and postoperative pattern of enteral feeding interruption, neonates with a minimally interrupted feeding pattern have PNI scores that fall above and below the cut-off value of 55 as proposed by Wakita et al (2011), therefore in this cohort, PNI does not appear to be prognostic of the pattern of postoperative feeding interruption.

Figure 4.4: Relationship between Onodera's Prognostic Nutritional Index (PNI), pattern of enteral feeding and feeding outcome



*PNI values not performed on N1, N12, N18

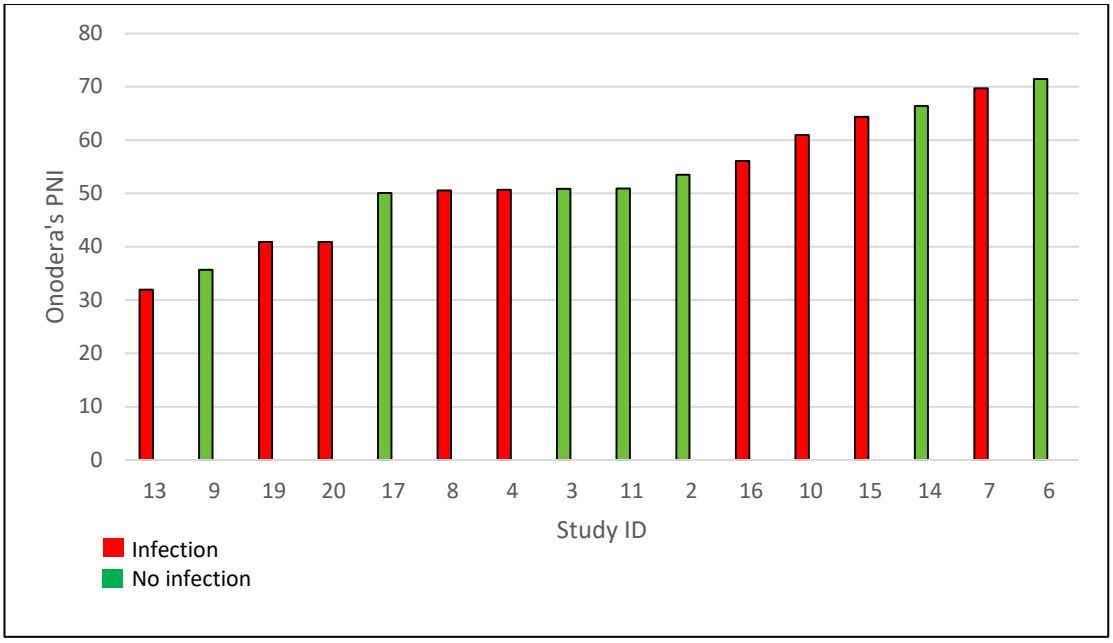
When looking at enteral feeding outcome, neonates who achieve oral feeding success (feeding outcome 1) after surgery are represented across the range of PNI values, as also demonstrated in Table 4.4. As can be seen, those neonates who fail to feed orally or to feed at all (feeding outcome 2 to 4) the range of PNI values are similar to the oral feeding group.

Postoperative infection was identified as the most commonly occurring complication after neonatal surgery with its incidence spread evenly across the range of PNI values as can be seen

in Figure 4.5. No predictive relationship was observed between low PNI scores and increased frequency of postoperative infection complications.

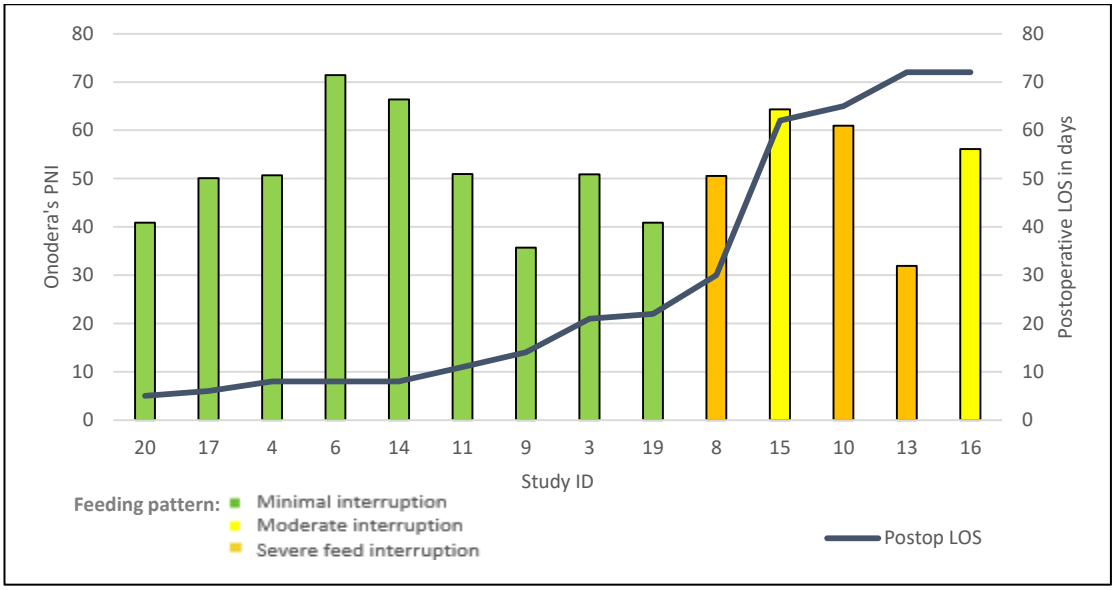
Similarly, when considering postoperative length of stay, the outcome most closely related to low PNI values in Wakita et al's (2011) study, for the neonatal population in this study there was no relationship seen to suggest PNI scores were associated with length of postoperative

Table 4.5: Relationship between Onodera's Prognostic Nutritional Index (PNI) and presence of postoperative infection



*PNI values not performed on N1, N12, N18

Table 4.6: Relationship between Onodera's Prognostic Nutritional Index (PNI) and absolute postoperative length of stay (LOS) for surviving neonates by feeding interruption pattern (ordered by increasing LOS)



*PNI values not performed on N1, N12, N18

stay (Figure 4.7). Onodera's PNI remains stable despite an increasing length of stay.

4.6 Discussion

4.6.1 Patterns of feeding

Similarities and differences between those neonates within the postoperative enteral feeding patterns identified in this study will be discussed first.

I. Weight-for-age *z* scores (WAZ)

The findings of this study demonstrated 11% of the neonates at birth had a WAZ score category less than -2 SDs, similar to the 12% incidence found in Study 2 (Chapter 3) and to the 12% and 16% reported by Di Maria et al (2013) and Ross et al (2017) respectively. By the time of surgery, one of these neonates had progressed into a normal category, with two normal weight neonates having dropped into an underweight WAZ category. Reasons for this are multi-factorial but are likely to include expected weight loss during the first week of life, preoperative requirement for intensive care with resulting sub-optimal nutrition, and timing of presentation. Although intrauterine growth retardation has been proposed as a possible component of low WAZ in a cardiac population (Malik et al, 2007; Mitting et al, 2015), the findings of this study do not suggest this played a significant part in this neonatal cohort.

Irrespective of initial WAZ category, all neonates experienced significant postoperative weight loss with growth faltering during hospitalization, despite only four neonates falling into an underweight WAZ category by the time of discharge. This occurred more frequently in those neonates with more interrupted enteral feeding patterns. This phenomenon has previously been reported in neonates with single ventricle physiology (Hehir et al, 2008) but was a common feature of all neonates in this study irrespective of diagnostic group and is consistent with the findings of Anderson et al (2011) in infants less than 6-weeks of age with two-ventricle physiology.

The findings of this study also demonstrated that for all neonates, whilst remaining inpatients with weight monitoring and access to specialist dieticians, signs of faltering growth were responded to and the in-hospital weight gain in tube-fed neonates was greater than those orally feeding. This is similar to the findings of Sables-Baus et al (2012) where neonates receiving oral feeds weighed less than counterparts with in-dwelling feeding tubes at time of discharge in a retrospective review of 56 survivors after both univentricular and biventricular surgical repair. This highlights a dilemma regarding the potential benefit of short-term better feeding and weight gain after surgery versus the known risk of gastro-oesophageal reflux,

aspiration and underdevelopment of oral feeding skills associated with tube feeding (Sables-Baus et al, 2012). Taken together, these findings reinforce the necessity for all neonates to receive careful postoperative nutritional and growth monitoring post discharge, particularly in those neonates with short hospital length of stays who may not have sufficient time to demonstrate sustained weight gain prior to hospital discharge, and for those on a univentricular surgical pathway, who are especially vulnerable to growth failure (Lambert et al, 2014).

Neonates who survived beyond ICU discharge, irrespective of their feeding interruption pattern, managed to achieve and maintain weight gain from the point of their lowest recorded postoperative weight, which for the majority was recorded at the time of intensive care discharge. This finding is consistent with patterns of postoperative weight loss previously published (Alten at al, 2015), which demonstrates that absolute weight gain prior to discharge is achieved but is often delayed whilst in an intensive care environment (Nicholson et al, 2013; Li et al, 2018). Taken together, this supports the existing body of evidence that any sick neonate requiring prolonged intensive care stay is extremely vulnerable to faltering growth (Valla et al, 2018). In addition, there are complexities in trying to estimate intensive care energy requirements that, in the absence of indirect calorimetry, are difficult to predict following cardiopulmonary bypass surgery, when the change from an initial post-bypass catabolic state to one towards recovery anabolism is uncertain. Added to which, this change may not be linear as neonates experience significant energy demands when moving from positive to negative pressure ventilation, irrespective of the impact of residual lesions causing significant heart failure as seen in one of the study participants. For any surgery performed during the first two weeks of life, when weight loss is expected following birth, determining additional morbid weight loss will prove challenging irrespective of postoperative feeding pattern.

II. Initiation of enteral feeding

The chronologies of neonates with minimally interrupted feeding displayed early feed initiation when compared to those neonates demonstrating more interrupted patterns of feeding. Early feed initiation is therefore likely to be representative of those neonates who were clinically and physiologically more stable after surgery. Despite feeding disruption occurring following initiation of enteral feeds in this group, durations of intensive care stay were short and no further feeding disruptions occurred following discharge to the ward. Consequently, they were viewed to be on a trajectory which would facilitate the early catch-up

growth reported in infants with complex congenital heart disease (Medoff-Cooper et al, 2016), although this could not be confirmed as part of this study.

The likelihood of successful oral feeding significantly decreased when there was a significant delay in time to feed initiation, which was a feature of those neonates falling into the most interrupted patterns of enteral feeding. This was usually seen in those neonates with higher surgical risk and higher intensive care admission severity scores (that is, a clinically sicker cohort). This pattern has previously been documented by Sables-Baus et al, 2012). Delays in initiating enteral feed were multifactorial and appeared somewhat dependent on the existence of acute post-operative complications (e.g. rhythm disturbance) leading to cardiovascular instability with the persistence of hyperlactataemia beyond an initial 48-hour postoperative period.

Both neonates who failed to receive any enteral feeds had the highest surgical risk with body weights at the lower end of the spectrum when compared to other neonates in the cohort. Both were entering a univentricular palliative surgical pathway with surgery having been delayed – in one to facilitate growth, and the other due to preoperative infection concerns. Refractory low cardiac output states and persistently elevated lactates to the time of death meant no attempt to introduce enteral feeds was made.

III. Disruption to enteral feeding

For those neonates experiencing significantly interrupted patterns of enteral feeding, the time to first feed was generally longer (reflecting a greater level of clinical instability) but, paradoxically, once feeds had commenced a lower percentage of total feeding disruption was experienced. However, a need for ongoing care within an intensive care or critical care environment led to slower feed advancement and poorer nutritional intakes. The likelihood, therefore, of successful oral feeding in neonates with patterns of increasing enteral feed interruption was more uncertain. This is consistent with findings from Indramohan et al (2017) in a study of 34 neonates and identified a longer duration of intubation (p=0.004) and an increased number of days when feeds were withheld postoperatively (p=0.001) and were both associated with failure to attain oral feeding by the time of discharge.

Insidious complications of uncertain aetiology which required re-intubation followed by multiple investigations (for example, in cases of phrenic nerve palsy) or the complete cessation of enteral feeding (for example, NEC) appeared unifying characteristics of those neonates with severely interrupted feeding. Both neonates suspected as having NEC were classified as Bell's Stage 1 – that is, a normal gas pattern or mild ileus with high gastric residuals and mild

abdominal distension (Gordon et al, 2007). However, unsurprisingly in a neonatal cohort reported to be at increased risk of this complication (Schuchardt et al, 2018) a cautious approach with cessation of enteral feeds and medical management was to be expected.

IV. Oral feeding success

By the time of hospital discharge, two-thirds (68%) of neonates were orally feeding. Although not exclusively a characteristic of those neonates with minimally interrupted patterns of feeding, all neonates in this group managed to achieve oral feeding success by the time of hospital discharge which generally occurred two weeks from surgery. This was in keeping with the median length of stay identified in Study 2, which was used to determine duration of follow-up for this study. This high proportion of oral feeding achievement is reassuring and reflects slightly better oral feeding outcomes than previously published studies in this area. Alten et al (2015) in a retrospective cohort study of 251 neonates from 21 North American hospitals voluntarily submitting cases to a clinical registry, described 56% orally feeding at discharge. Natarajan et al (2010) in a retrospective chart review of 67 neonates reported 54% of those surviving (n=63) to be on complete oral feeds at the time of discharge. Sables-Baus et al's (2012) study of 56 neonatal survivors following cardiac surgery reported similar findings with an oral feeding success rate of 57%. Although their cohort had a high incidence of prematurity (25%) and lower use of cardiopulmonary bypass surgery (40%), of note 75% underwent surgery within the first week of life with 45% having required preoperative mechanical ventilation. Preoperative oral feeding opportunity was consequently low and this may have had an important impact on successful oral feeding outcome (Sables-Baus et al, 2012). In comparison, the findings of this study were that some preoperative oral feeding was achieved to some extent in 14 of the 17 surviving neonates (82%), with 5 (29%) exclusively orally feeding prior to surgery. This may have permitted the early establishment of co-ordinated oromotor feeding skills, which is known to be problematic in this patient population after surgery (Sables-Baus et al, 2012; Pereira et al, 2015) and these prior experiences may have contributed to the better oral feeding outcomes seen postoperatively.

The variation in oral feeding success found between this study and previously published literature may be due to differing thresholds for feeding intervention, or differences in follow-up duration, as practice variation was identified by Alten et al's (2015) study, despite the similar reporting of length of hospital stay. As the majority of previously published work regarding postoperative neonatal feeding following cardiac surgery is North American in origin, there may be institutional as well as organisational differences in the model of postoperative care delivery from the current UK model. In the latter, following extubation neonates are

transferred to cardiac wards able to provide some form of high-dependency care for those neonates receiving weaning doses of inotrope and high-flow oxygen administration. Only one study (Nicholson et al, 2013) was found to report ICU and hospital length of stay separately.

Successful oral feeding outcome after neonatal cardiac surgery is an important finding. Tregay et al (2015) have reported feeding difficulties and the need for gastrostomy placement as risk factors for both unplanned re-admission and mortality following major cardiac surgery in early infancy. Two-thirds of parents whose baby was readmitted to hospital reported the feeding of their child to be one of the most stressful and demanding aspects of post-discharge care (Tregay et al, 2017). Therefore, having a baby who is feeding 'normally' after surgery is likely to significantly reduce both the physical demands inherent with supplemental tube feeding and reduce the psycho-emotional impact of having a baby who is a poor feeder during this vulnerable post-discharge period (Brown & Smith, 2018; Jackson et al, 2018).

For the three neonates with hypoplastic left heart syndrome (diagnosis category 4) entering a palliative single ventricle surgical pathway, feeding outcomes were poor. Two of these neonates required placement of a gastrostomy tube, both occurring outside of the period of active follow up, and one neonate failed to achieve any enteral feeding prior to death on postoperative day 32. This is consistent with previously published studies following staged single-ventricle palliation where the likelihood of successful postoperative oral feeding is particularly bleak. Hebson et al (2012) found only 26% of 334 neonates fed by mouth at the time of hospital discharge, with feeding dysfunction persisting at or beyond 2-year follow-up (Maurer et al, 2011, Hill et al, 2014). This finding is of consequence, as Williams et al (2011) reported a higher incidence of post-discharge growth failure in their tube-fed univentricular population than those who managed to feed orally, which at time of second stage surgery is known to be associated with poorer surgical outcomes (Anderson et al, 2011). A hypothesis presented was that a failure to feed orally in association with poor inter-stage weight gain were indicative of a more brittle univentricular circulation.

V. <u>Feeding patterns and postoperative complications including infection</u>

The presence of postoperative complications appeared to be the most significant factor that determined the eventual pattern of feeding. The majority of neonates with severely interrupted feeding had early postoperative courses which would not have predicted them to be at nutritional risk. However, it was a failure to progress and wean from mechanical ventilation after surgery which appeared to have most influence on feeding outcome. This is in keeping with a study by Larsen et al (2013) who determined that those neonates with the lowest energy intakes postoperatively experienced longer durations of mechanical ventilation,

had longer intervals between surgery and delayed sternal closure, and more delay until first feed and achieving full feeds. Prolonged intubation, intensive care readmission and a requirement for further cardiac reintervention whilst on intensive care were prominent features determining eventual feeding patterns, and all were seen in association with postoperative complication.

Unplanned postoperative cardiac reintervention has been associated not only with increased mortality but with increased duration of intensive care length of stay (Mazwi et al, 2013; Costello et al, 2018; Brown et al, 2003). This reinforces the significant impact that residual lesions have by increasing the requirement for intensive care, a factor already known to compromise adequate nutritional delivery (Mehta et al, 2012). Investigations and multiple failed extubation attempts were the most frequent causes of feeding disruption in this study, consistent with the findings of Keehn et al (2015) that prolonged initiation and avoidable disruptions are responsible for the already tenuous feeding achievements seen within intensive care settings.

Taken together, this suggests that attempts to minimise complications, and aggressively manage them when they do occur, could lead to improved nutritional outcomes. In those neonates requiring cardiac reoperation and diaphragm plication whilst on intensive care, surgeries did not occur until postoperative day 32 and 35 respectively, with operations delayed for the treatment of contemporaneous infection-related complication. This is an important finding as Pasquali et al (2013) have reported infection complications are significantly associated with increased mortality and prolonged postoperative length of stay.

Mazwi et al (2013) identified that timing of reintervention is an important predictor of subsequent morbidity. Where prompt addressing of residual lesions within two days of the initial surgical procedure occured, lower mortality and shorter length of postoperative stay was seen than in those reinterventions which occurred 8 to 18 days afterwards. Findings from this study confirm prior findings, as it was those neonates where clinical trajectory stalled who were seen to experience cumulative morbidity, including infection related complications, from the protracted stay in intensive care that resulted. As earlier reintervention has been shown to lead to shorter duration of intensive care stay it is feasible that other aspects of postoperative care, including nutritional status, could see similar benefits. Blinder et al (2017) have demonstrated that increasing duration of mechanical ventilation is associated with increased likelihood of postoperative complications and findings from this case-study appear to support this. Those neonates without preoperative risk factors and receiving optimal care (that is, a technically competent operation with no residual lesions) generally experienced short

durations of mechanical ventilation and few postoperative complications even when undergoing relatively high risk operations. Consequently, for these neonates both surgical and nutritional outcomes, as reflected by minimal enteral feeding interruption and successful oral feeding at discharge, were very good.

Of particular interest, in those neonates with minimally interrupted feeding and successful oral feeding, complications were infrequent and when they were seen were mainly related to wound healing, diagnosed as being localized wound dehiscence, stitch abscess or superficial wound infection. In all bar one case, the complication occurred following hospital discharge. In contrast those neonates with longer lengths of stay who experienced multiple morbidity, incidence of superficial wound infection was low although rates of more significant infection (for example, sepsis, blood stream infection and mediastinitis) appeared to increase. Antibiotic use outside of accepted surgical prophylaxis was a feature of all neonates with extended length of stay and, paradoxically, this may have minimized their risk of superficial surgical site infection, introducing the possibility of competing risk, where antibiotic treatment for one infection protects against another from occuring. Therefore, a complex and not entirely discernable multi-factorial relationship appeared to be evident between infection-related complications and length of stay, and appeared to be associated with poorer nutritional outcome.

Study 2 findings demonstrated a relationship between methicillin-sensitive Staphylococcus aureus carriage and surgical site infection. In this study one neonate (8%) was identified as being a preoperative carrier of MSSA through formal screening which occurred in 13 of the 19 included neonates, consistent with current evidence regarding rates of neonatal carriage (Jimenez-Turque et al, 2016). However, six neonates were not screened in line with current guidelines which gave a poor compliance rate for preoperative screening at 68%. As Staphylococcus aureus was the pathogen causing subsequent health-care associated infection in half of these unscreened neonates, this is a significant finding which needs to be emphasized, as preoperative decolonization for a positive carriage state may have modified this result.

4.6.2 Barriers to enteral feed progression

Elevated serum lactate concentrations were identified as the primary reason why enteral feeds were withheld, and lead to delay in excess of 24 hours in the initiation of enteral feeds for 47 % of the cohort, and in excess of 48 hours in 26%. Although serum lactate levels and high inotropic requirements were often associated, it appeared that the strongest predictor of

enteral feeding was a lactate level less than 2 mmol/L. During periods of prolonged starvation, an absence of trophic feeding was also observed.

Hyperlactataemia results from anaerobic metabolism in response to inadequate cellular oxygen delivery and is often used as a biomarker of oxygen delivery and circulatory status (Toda et al, 2005). As mesenteric hypoperfusion is believed to be a possible contributor to NEC in neonates with CHD (Scahill et al, 2017), it is understandable that there will be a reluctance to feed when splanchnic circulation may be further compromised by high vasopressor use postoperatively, as reflected by the high VIS scores in this study. As serum lactate is used as a surrogate marker for tissue hypoxia and inadequate perfusion (Aly et al, 2016), and in addition elevated levels continue to be associated with poorer outcomes after paediatric cardiac surgery (Maarslet et al, 2012; Schumacher et al, 2014; Kanazawa et al, 2015) it is unsurprising that it is also perceived to be a risk factor for NEC.

In terms of adherence to unit specific enteral feeding guidance, caution in certain groups of postoperative cardiac patients is advocated but withholding feeds with elevated lactate levels is not specified. The medical literature evaluating the use of enteral nutrition and vasoactive substances in haemodynamically unstable patients is lacking, but in clinical practice enteral nutrition is withheld in patients on vasoactive substances most often on the assumption that in haemodynamically unstable patients, enteral nutrition will increase splanchnic oxygen demand which when the body is unable to meet this demand, will lead to splanchnic ischaemia (Allen, 2012).

The precise aetiology of elevated serum lactate has been ill-defined but is hypothesized to signal hypoxia and hypoperfusion states (Mak et al, 2016). Usual clinical indicators of adequate tissue perfusion, such as normal blood pressure, cardiac output, and urine output, are often believed to be misleading in the face of high circulating lactate levels (James et al, 1999). Following periods of ischaemia and circulatory arrest on cardiopulmonary bypass elevated serum lactate levels are expected, as are concerns over hypoxia and reperfusion-injury. Indeed, in a recent cross-sectional survey of feeding practices in infants with CHD across European ICU's serum lactate was a variable quoted 62.5% of the time to assess readiness for and tolerance of enteral feeds (Tume et al, 2018). In the absence of evidence to the contrary, it is likely that caution in enteral feeding will continue to be exercised, as on balance it is viewed as being less harmful than the potential risk of NEC, and as such cannot be viewed as a readily modifiable factor in mitigating the longer-term effects of underfeeding in this population.

Postoperative fluid restriction following cardiopulmonary bypass was also found to be a barrier to initiating enteral feeds, as intravenous medication would often exceed the daily allowance as stated in the fluid administration regime. This has previously been identified by Wong et al (2015) as the single most important barrier to nutrition post cardiac surgery, leaving little room for nutritive feeding. In comparison with published research from other cardiac centres, the current post cardiac surgery fluid regime was more restrictive at initial maintenance fluids at 25% on day of operation, with liberalization by 25% per day increments until maximum intravenous maintenance of 100ml/kg/day is reached on postoperative day 3. Guidelines from other centres vary, with initial volumes on day of surgery reported at 40-50% maintenance (Nicholson et al, 2014); 50% maintenance (Shann et al, 2008); and two-thirds maintenance with subsequent liberalization over the first postoperative days (Li et al, 2018). This suggests in the current era with newer techniques such as modified ultrafiltration to overcome the dilutional effect of the cardiopulmonary bypass circuit (particularly in neonates), the departmental fluid restriction regime should be liberalized, thus making 'room' for enteral feeding. This would appear prudent, as study findings revealed no neonate achieved the fluid restriction target in the first 48 hours after surgery.

Despite a feeding protocol that advocates the use of trophic feeding, in addition to IV fluid allowances, this was not routinely applied to any neonate in this cohort, where there was very low use of trophic feeding. There were only two instances when trophic feeds were commenced in neonates unable to start enteral feeding of nutritional value. Although the rationale was clear in one neonate with a suspected surgical abdomen on parenteral nutrition (Surgeon request), the reason for starting in the second neonate was not clear although inotrope score and lactate indicated that there would be a delay before enteral feeds would be considered. This appeared a proactive choice for enteral feeds, and the result of an individual's clinical decision rather than unit practice. Despite increasing evidence that trophic feeding may be of benefit in maintaining bowel wall integrity and reducing gut translocation of bacteria and potential risk of multi-organ system failure (Ibsen et al, 2006), there was little demonstration that this approach had been embraced into postoperative cardiac neonatal care, particularly when the theoretical risk of NEC is greatest. Rather, apart from in this one instance, an extremely cautious approach to trophic feeding appeared to be evident which may be linked to the severity of the fluid restriction decreasing the likelihood of trophic feeds being commenced.

Wong et al (2015) also identified feed disruption as another important barrier to optimal nutrition following paediatric cardiac surgery. In this study, feed disruptions occurred on 135

days out of the total 382 enteral feeding days, equating to a disruption rate of 35% which was higher than the 21% reported in Schwalbe-Terrili et al's (2009) study. The majority of the disrupted feeding days occurred whilst on the intensive care unit, and many extended periods of starvation were airway-related in terms of NBM times prior to extubation with slow reintroduction of enteral feeds following extubation. In addition, episodes of starvation were associated with procedures where unit guidance does not specify a nil by mouth requirement, and this study highlighted this as being the most discrepant aspect of practice. For example, all neonates were placed nil by mouth for delayed sternal closure rather than stopping feeds immediately prior to the procedure with the aspiration of gastric contents, as advocated by the unit guidelines. Reasons for this discrepancy remain unclear, as data collection methodology was unable to identify whether this decision was ordered by the surgical team or made by the bedside nurse. Strategies to reduce these unnecessary occurrences should be explored as a mechanism for enteral feed improvement. Additionally, following periods when feeds were ceased for a procedure or extubation, subsequent feeding rates were not increased to compensate for the missed feed volume, with intravenous fluids being administered instead. In addition, in many instances, feeds were graded back from a lower rate rather than resuming feeds at the previously tolerated rate. Keehn et al (2015) identified that lost nutrition not replaced during times of feeding results in patients receiving only 55% of their energy requirements. As this was a common feature seen across all neonates these missed opportunities for feeding could easily be addressed by the introduction of a neonatal feeding protocol.

Postoperative complications which necessitated longer durations of intensive care stay significantly impacted on the ability of neonates to advance to full enteral feeds. The concept of the 'domino effect', where several postoperative complications occurring together in the same patient has a considerable effect on increasing length of stay, has previously been reported in the literature (Brown et al, 2003). This phenomenon was in evidence within this cohort study. In addition to a lengthened intensive care stay those neonates failing spontaneous breathing trials, requiring multiple reintubations and/or reoperation not only demonstrated the most interrupted feeding patterns, but also experienced more healthcare associated infection-related complications than their counterparts, which placed them at further nutritional risk over and above that inherent with being an inpatient on intensive care (Velazco et al, 2017; Keehn et al, 2015; Mehta et al, 2012). As fever is associated with infection, there is an increased metabolic demand placed on the neonate which further impacts on the availability of those nutritional substrates required for growth. An aggressive

strategy of excluding or treating possible complications whenever a patient deviates from a normal postoperative course has been proposed in order to minimise this domino effect (Brown et al, 2003).

4.6.3 Onodera's Prognostic Nutritional Index as a predictor of postoperative feeding

Findings from this study do not support the use of Onodera's PNI as a prognostic tool in identifying neonates undergoing cardiac surgery who may be at additional risk of postoperative adverse outcomes. In addition, there appeared to be no relationship between preoperative feeding volumes and calculated Onodera's PNI, which makes its reliability as an indicator of nutritional status in this cohort questionable.

Fluid resuscitation of those neonates with a postnatal diagnosis, having presented in cardiovascular collapse, will alter baseline albumin and lymphocyte levels, but often volume resuscitation is albumin which may lead to erroneous assessment of true albumin levels especially as the last recorded preoperative blood results were used to calculate PNI. Serum albumin, forming part of the index equation, has commonly been used as a preoperative biomarker of nutritional status and associated with postoperative outcome (Leite et al, 2005) despite an approximate 2-week half-life, which firstly, may not reflect acute depletion of protein intake post-partum. Secondly, albumin is often the fluid resuscitation of choice in neonates, and therefore levels may have reflected exposure to donated albumin in those neonates presenting in cardiovascular collapse and managed on intensive care prior to surgery. Sick neonates will be predisposed to low albumin states as it is a negative acute phase protein, which in times of stress and inflammation is down-regulated, allowing preferential production of CRP and fibrinogen (Briassoulis et al, 2001). These factors may have had an unknown but significant impact on preoperative albumin levels in this study, affecting the reliability of Onodera's PNI. As albumin levels are also affected by dehydration (Mehta & Duggan, 2009), both preoperative diuretic use and fluid restriction may also have impacted on serum albumin levels. However, this remains purely speculative as data regarding pre-operative diuretic and fluid restriction were not collected as part of this study.

Identifying preoperative malnutrition in cardiac children who have been reported to be at additional risk of postoperative complication (Ross et al, 2017) is an attractive idea, which could potentially be useful in improving clinical outcomes if nutritional interventions could be modified preoperatively to target this. Although Wakita et al (2011), in their study of 36 infants undergoing cardiac surgery with a median age of 5.8 months (± 6.2), reported a positive finding using Onodera's PNI at a cut-off value of 55 the best predictor of length of stay, the

applicability of this index in a purely neonatal population is not supported from the findings of this study.

4.6.5 Overall summary of findings

Postoperative weight loss was observed in all neonates, with slow progression of enteral feed volumes during the first week after surgery. However, a similar decrease in weight-for-age z-score category was not seen, suggesting weight decreases are related to transient inadequacies in nutritional intake. Weight gain was not demonstrated in these neonates until adequate feed volumes were achieved, which only occurred after intensive care discharge. As has previously been reported, postoperative weight gain in the intensive care unit is certainly limited by the profound metabolic and hypercatabolic response to cardiopulmonary bypass and injury (Toole et al, 2014). Limited amounts of nutritional intake were seen immediately following cardiac surgery, primarily related to elevated lactate levels, haemodynamic instability and fluid restriction, but exacerbated by unnecessary feed disruption in association with procedures or diagnostic testing.

4.6.6 Limitations

This was a single centre study in a defined group of term neonates requiring congenital heart surgery and almost exclusively prostaglandin dependent preoperatively. Therefore, data from this population previously identified as being at risk for postoperative complications may not be generalizable to other older children with other types of structural congenital heart disease. In addition, there was a lower prevalence than expected of genetic syndromes (for example, Trisomy 21 and 22q11 deletion) associated with cardiac pathology which might be expected to adversely affect feeding outcomes, which may have resulted in better oral feeding outcomes than has previously been reported.

Although a prospective study design was chosen to improve the overall quality of data, the intermittent nature of data collection may have led to the potential omission of pertinent patient data not known or measured during the active periods of data collection. As a result, this may have adversely affected the richness of the neonatal chronologies from which patterns of feeding were identified. It is recognised that a more continuous method of data collection may have identified additional variables, but it is unlikely that any additional data would have altered the feeding categories the neonates were assigned to.

Additionally, some neonates were found not to have had their weight documented on the day of hospital discharge, therefore growth velocity was subsequently calculated using the last

postoperative weight available, which may have impacted on findings by underestimating true growth velocity.

The study used a weight-based measure in isolation to assess nutritional status postoperatively, and it is recognised that although this may be a frequent and easily measurable marker of nutritional status, acute weight changes may be more reflective of changing fluid status in cardiac neonates, especially in the immediate postoperative period (Schwalbe-Terilli et al, 2009). Fluid shifts, capillary leakage, and oedema may also confound weight-based anthropometric indices (Ross et al, 2017). Additionally, for those infants with shorter lengths of postoperative stay, incidence of continued diuretic use at discharge may have adversely affected discharge weights than for those neonates where prolonged hospitalization for complications may have resulted in the cessation of postoperative diuretic therapy prior to discharge. Therefore, including a weight-based data collection point at the time of first follow-up after discharge may have provided a more complete trajectory of postoperative weight gain, and enabled assessment of longer-term feeding achievement, and validation of allocation to the feeding interruption categorisation process.

For those babies operated on within the first two weeks of life, weight measurements may have been confounded by the physiological weight loss experienced by all neonates following birth. This postnatal diuresis is associated with contraction of the extracellular fluid compartment due to the loss of isotonic fluid from the interstitial fluid compartment, typically resulting in a reduction in body weight of 5 – 10% in healthy term babies. Consequently, weight is usually at its nadir around day 5 of life, with most babies regaining their birth weight between 7 and 10 days (O'Brien & Walker, 2014). However, equivalence in cardiac neonates is unreported.

Finally, in neonates, unless small for dates, anthropometric indications of growth failure may not appear preoperatively even when subjects are under surgical stress or have inappropriate nutrient intake preoperatively. Malnutrition in this age group is relatively less common than in older children with cardiac disease because the intra-uterine environment will provide nutrients and consequently will afford some early protection. Therefore, using absolute weight-for-age z-score as the outcome variable in this study, rather than the degree of change, may have under-estimated the number of infants experiencing faltering growth (that is, a weight deceleration greater than 1 z-score), which may be a more sensitive indicator in identifying and targeting those neonates at nutritional risk.

4.6.7 Implications for practice

Findings from this study raise important aspects of clinical care which have implications for future practice.

Firstly, there is evidence that the existing postoperative fluid restriction regime is excessive in comparison to other centres, as well as findings which demonstrate it is not achievable in a neonatal cardiac surgical population when essential intravenous medication alone exceeds the stated allowance. The observed effect of the regime in clinical practice is that fluids are being restricted rather than liberalised in the days following surgery, and for the majority of neonates who experienced minimally interrupted feeding patterns, this meant that although enteral feeds had been initiated early, they were only marginally above trophic volumes by the time of intensive care discharge. Opportunities to maximise enteral feed intake would be more than doubled if a more liberalised fluid regime was adopted, which might mitigate against some of the postoperative weight loss observed.

Secondly, if compliance with existing unit feeding guidelines for procedural-related feed disruption improved, the amount of days and duration of unnecessary feed disruption would reduce. The study found all neonates being placed nil by mouth for delayed sternal closure, rather than the recommended cessation of feeds at the time of procedure with simultaneous aspiration of gastric contents. As timing of surgical procedures are often difficult to predict, and in this population are carried out between scheduled operations, the duration of the unnecessary starvation is further increased. In this era of electronic communication, reinforcing existing guidance amongst the unit nursing and medical staff via email may be sufficient a reminder that a period of pre-procedural starvation is not necessary, especially when feeding volumes are likely to be of little significance in neonates with a protected airway and confirmed endotracheal tube position. This would likely facilitate progression of enteral feeding in a timely manner and achieve greater feed volumes at time of intensive care discharge, which may lead to earlier establishment of full nutritional requirements and earlier discharge home. It may also make it easier to distinguish between situations of true feed intolerance versus lack of oral feeding practice.

A surprising finding was the absence in some of the neonates of a recorded weight measurement on the day of hospital discharge. Daily weight in children with congenital heart disease has been a mainstay in guiding the clinical decision-making regarding postoperative fluid status and requirement for ongoing diuretic therapy, in addition to ascertaining postoperative weight gain. It is recognised that the absence of a recorded weight on a hospital information system may not equate to a weight not being measured, but for a population

known to be particularly at risk of poor growth, this was an unanticipated and unexpected finding. However, reinforcement of the importance of this essential aspect of pre-discharge care should be readily amenable to improvement.

Lastly, although the intensive care unit has enteral feeding guidelines which have been shown to improve enteral feeding practices on the unit in children from other specialties (Tume et al, 2010) there has been little improvement within the cardiac population in general. Despite general nutrition guidelines being in existence, they do not account for the particular challenges faced by neonates following cardiac surgery, particularly with reference to guiding nursing decisions to initiate, progress or disrupt enteral feeding when inotropic and lactate levels are high. Similarly, guidance regarding trophic feeding in cardiac neonates does not go beyond exercising 'extreme caution' following coarctation and aortic arch repair due to the high risk of NEC. In the absence of further guidance, this caution appears to have been extrapolated to all neonates after cardiac surgery. Consequently, there is opportunity to develop clear guidelines for this sub-group of the paediatric cardiac surgical population, incorporating when, how, and what volumes to feed in the early postoperative period, which may be of benefit in optimising missed opportunities to enterally feed this vulnerable group.

4.6.8 Implications for future research

This study has presented the trajectory of enteral feeding for a small cohort of neonates following cardiac surgery. Feeding related endpoints up to the time of hospital discharge have been explored, and patterns of feeding interruption have been identified. However, the relationship between these early feeding experiences and longer-term growth and feeding outcome was beyond the remit of this study but remains as an important question in identifying whether the degree of feeding interruption experienced as a neonate is associated with later faltering growth or feeding dysfunction, and if the categories of feeding identified predict later growth success or failure. Longitudinal follow-up of this, and other cohorts, would provide rich data regarding not only early postoperative feeding experience but in addition its effect on longer term growth, contributing to an ongoing infant and childhood chronology which may provide a better understanding of the phenomenon of how catch-up growth occurs in cardiac children, and identify those children at risk of ongoing growth faltering despite surgical intervention.

Parental concerns regarding their child's feeding has already been identified as a significant stressor following discharge home (Tregay et al, 2017) with parental stress and coping having a powerful impact on the feeding process (Maurer et al, 2011). Caregiver concerns may negatively affect parent-child interactions around feeding and might exacerbate feeding

dysfunction, as seen in healthy children when higher intakes are promoted by mothers of infants and young children who refuse to eat (Wright et al, 2006). Hill et al (2014), in a cohort of single ventricle patients at 2-years of age, described a ten-fold increase in the incidence of parental aversion to mealtimes in children with single ventricle physiology compared to normal controls, in addition to the child manifesting significantly more mealtime aggression and resistance to eating than their healthy counterparts. Both situations are a likely response to high promotion of intake which may ultimately result in altered patterns of bonding and attachment. Exploring these relationships through qualitative study further may reveal strategies for multi-disciplinary interventions that facilitate parental coping, especially as Majnemar et al (2009) describe a high prevalence of neurodevelopmental, functional and behavioural problems after neonatal cardiac surgery which persist to early school age. Increasingly, there is a suggestion that difficult and lengthy hospital admissions after neonatal cardiac surgery are likely to precede difficult and lengthy journeys once the infant is home and this warrants further investigation.

4.7 Conclusion

In a cohort of neonates with isolated cardiac defects undergoing surgery, generally born at normal weight with normal weight-for-age z-scores, postoperative faltering growth was prevalent. Energy and protein delivery was inadequate, with the main barriers to nutrition identified as elevated postoperative serum lactate concentrations and high inotrope requirements, leading to significant delay in the initiation of enteral feeds. A strict fluid regime, unachievable in all neonates during the first 48 hours after surgery, served to prolong the period of inadequate nutrient delivery once cardiovascular stability had been achieved. In addition, unnecessary starvation for postoperative procedures outside of existing unit guidelines further compromised neonatal nutrition.

Nutritional feeding on intensive care was, unsurprisingly, significantly lower than that achieved following transfer to the cardiac ward, thus, when postoperative complications extended the duration of intensive care stay, this finding was heightened and feeding outcome worsened. A clustering effect of increased postoperative complication, significant infection, poor feeding outcome and increased length of stay was observed.

Nonetheless, the majority of neonates in this study achieved oral feeding success which is likely to minimise any potential long-term effect of transient weight loss. However, from this study it was evident that there are missed opportunities to optimise enteral feeding whilst on intensive care, and these should be addressed as a matter of priority.

Despite retrospective evidence suggesting early feeding does not increase incidence of postoperative NEC a cautious approach continues to be exercised. In the absence of robust data this caution is perhaps warranted in this vulnerable population. However, a degree of clinical equipoise will make it difficult to explore this phenomenon with prospective investigation.

Better ways for assessing preoperative and postoperative nutritional status are needed. Biomarkers of nutritional status, although appealing, have not been found to be nutrition-specific or resistant to the influences of stress, the inflammatory cascade or dehydration. Furthermore, none have been found which consistently predict intensive care outcome. Onodera's PNI was not of value in predicting those neonates with poorer outcome.

Chapter 5: Synthesis

5.1 Introduction

The aim of the studies presented in this thesis were to explore the relationship between nutrition and infection in children after cardiac surgery, with the underlying hypothesis that undernutrition may predispose children to increased risk of postoperative infection complications. Hospital acquired infection is a leading cause of morbidity and, in addition, not only places an additional financial burden to the NHS for related prolonged hospitalisation and readmission (Coello et al, 1993; DH 1995, 1995) but also readmission has social and emotional consequences for families which have only recently been reported (Tregay et al, 2016). Consequently, identifying modifiable risk factors for infection-related complications was felt to be important as these could potentially lead to alterations in the way children are cared for prior to and after surgery, with subsequent risk reduction.

This chapter will discuss the themes generated from the individual strands of research. Original contributions to knowledge will be presented, prior to a discussion of the strengths and limitations of the study. Finally, recommendations for further research, clinical practice and policy will be addressed, prior to a concluding statement.

The discussion will be divided into sections, synthesized from and structured around the themes identified through all the stages of the research, and presented in the context of recent relevant literature. The two key themes which are addressed are risk factors for postoperative infection, and the relationship between infection and undernutrition particularly in view of definitional inconsistencies within the literature.

The chapter commences with a summary table (Table 5.1) which provides an overview of the key findings from each of the three studies which are of relevance to the synthesis.

Table 5.1: Summary of key findings

Study	Key findings
Systematic review	Low quality evidence suggesting a tentative relationship between undernutrition and postoperative infection-related complications. Evidence lacking in neonatal surgical populations.
Retrospective cohort study	Neonates had the highest risk of surgical site infection (SSI). Most SSI was superficial. Low weight-for-age scores were highest in the infant age group, whereas the majority of neonates were of normal weight at birth and time of surgery. Staphylococcus aureus carriage was identified as being the only modifiable preoperative risk factor for SSI.
Case study	Patterns of feeding after surgery appeared predictive of length of stay, oral feeding outcome and postoperative complications including infection. Isolated wound dehiscence and superficial SSI was seen in those neonates with the shortest hospital stays. Clustering of postoperative complications appeared associated with significant infection (i.e. not superficial SSI), increased length of stay and poor feeding outcomes.

5.2 Risk factors for postoperative infection complications

5.2.1 Age

The findings from this study confirm neonatal age is a highly important factor determining postoperative infection complications in children after cardiac surgery. This is in keeping with the body of published literature (Allpress et al, 2004; Sarvikivi et al, 2008; Ben-Ami et al, 2008; Sohn et al, 2010; Barker et al, 2010, Costello et al, 2010).

In addition to infection complications, an association was found in both the retrospective audit and case study with higher morbidity and increased length of stay in this neonatal population, which is in keeping with previously reported outcomes in this age group (Mitting et al, 2015). Cardiac neonates in Study 3 whose initial presentation was with cardiovascular compromise and end-organ dysfunction, and who required preoperative mechanical ventilation and resuscitation prior to surgery, were found to have worse postoperative outcomes than their antenatally diagnosed counterparts who were cared for preoperatively in a ward environment. This is consistent with previous studies reporting increased duration of postoperative mechanical ventilation, increased rates and severity of end-organ dysfunction; increased infection and increased mortality are associated with the late-diagnosis of congenital heart

disease and the need for preoperative mechanical ventilation (Brown et al, 2003; Simsic et al 2007; Iliopoulos et al, 2016).

There are numerous reasons why neonates are at higher risk. They are more likely to undergo complex operations, have longer cardiopulmonary bypass (CPB) times, greater haemodilution due to circuit volume and operative hypothermia will often be associated with periods of circulatory arrest which account for these outcomes (Williams et al, 1998). Following CPB at any age there is a cascade of cytokine-mediated inflammatory responses following cell activation upon contact with the extra-corporeal circulation (Sonntag et al, 1998). The smaller the patient, the greater the exposure to the artificial surface of the circuit (El Habbal et al, 1995; Blackwood et al, 2010), therefore, the more profound this response is likely to be. Clinically this will manifest in a greater systemic inflammatory response affecting multiple organ systems and prolonging the requirement for intensive care compared to older children.

In addition, there is known immaturity of the neonatal immune system with neutrophils demonstrating weak bactericidal function and poor response to inflammatory stimuli (Nussbaum et al, 2013). Monocytes and macrophages are also immature, resulting in reduced cytokine responses compared to adults and consequent poor tissue repair and impaired phagocytosis of potential pathogens (Simon et al, 2015). This positions neonates as being at increased risk of bacterial infection, especially during the first month of life when circulating complement component levels are low, co-existing with low immunoglobulin concentrations (McGreal et al, 2012).

Nutrient-immune interactions are of special concern in neonates because of the increased vulnerability of the developing immune system (Kleinman & Greer, 2013). There is evidence that human milk plays an important role in developing immunocompetence; in early life systemic humoral immunity is strongly dependent on maternal secretory Immunoglobulin A supplied by breastfeeding (Kleinman & Greer, 2013). The reliance on maternal factors may be compromised in cardiac neonates when feeding volumes are withheld or insufficient, and this may account for some of the worse outcomes reported in units not allowing preoperative enteral feeds (Alten et al, 2015), with the suggestion that undergoing early complex cardiac surgery may disrupt the physiologuic maturation of the feeding milestone (Sables-Baus et al, 2012). Results from the case study demonstrated the study hospital promoted the use of breast milk and achieved preoperative feeding at full enteral volumes in stable, ward-based neonates. This approach may have contributed to the better feeding outcomes observed compared with reports from other units.

The urgent nature of most neonatal cardiac surgical operations, however, will mean that as an independent risk factor, age is not readily amenable to modification. Nonetheless, there is a suggestion from both study findings and existing literature that there may be some benefit in how neonates are cared for pre- and postoperatively which might mitigate some of this risk. These factors will be discussed further in later sections.

5.2.1.2 Reoperation

Study findings from the retrospective audit suggested an increased risk of surgical site infection in children having three or more planned cardiac operations (OR 4.9, 95% CI 1.19 – 20.49), with results from the case study suggesting those neonates experiencing unexpected reoperation were at increased risk of postoperative infection complications.

Cardiac reoperation has previously been identified as a risk factor for surgical site infection (Barker et al, 2010; Stey et al, 2014), as well as increased surgical risk related to complications that may arise while trying to enter the mediastinum during redo sternotomy. These include severe haemorrhage and injury to the cardiac chambers, major vessels, and previously placed shunts or conduits (particularly if these structures are in the immediate proximity to the back of the sternum). Retrosternal adhesions from prior surgery are thought to significantly increase the risk of complications (Adibi et al, 2014). With this major risk of bleeding, transfusion requirements can be significantly increased, and although not considered a variable in the retrospective audit, was found to be associated with poor outcome in the one case study neonate who experienced severe bleeding. In keeping with the published literature, this neonate experienced mediastinitis which Costello et al (2010) has previously reported, with an increased length of time ventilated which has been previously identified by Blackwood et al (2010).

However, reports of transfusion related complications accounting for poorer outcomes within the literature are inconsistent. A randomized controlled trial by Lacroix et al (2007) comparing a restrictive versus liberal transfusion strategy (thresholds of 7g/dl versus 9g/dl) in 626 children on a paediatric intensive care unit found no difference in outcomes for nosocomial infection, duration of mechanical ventilation or length of intensive care unit stay. Although cardiac surgical patients were represented (comprising 20% of patients in both arms) the overall sample size may have been too small to permit a definitive conclusion.

The cardiac reoperation rate identified in the retrospective audit was 5.3%, of which 4.4% was planned and 0.8% unplanned occurring during the same hospital admission. In the case study one of the 19 neonates required reoperation (5%) due to a residual lesion. Reoperation is not

uncommon in children undergoing cardiac surgery for congenital heart disease with a rate previously reported as 15% in operative survivors during a 25-year period having up to 26 years of follow-up (Monro et al, 2003). This study included 1220 consecutive paediatric cardiac surgical patients operated on between 1976 and 2001 by a single surgeon in one centre. Planned reoperations accounted for 78% of this rate, with 22% being unexpected. Certainly, the reoperation rates observed during the retrospective review appear favorable in comparison, although the ratio between planned versus unplanned remains consistent. Advances in surgical strategies and approach during the intervening years may have contributed to the lower incidence, in addition to a shorter duration of overall follow-up.

Data demonstrate an association between reoperation and increased infection complication, irrespective of whether planned or unplanned and time duration between surgeries. However, whether this was causal or associative remains unclear from this observational study but certainly warrants further investigation. However, the nature of neonatal cardiac surgery means all reoperation is unplanned, therefore this does not fully account for the increased risk of infection found in this age group.

5.2.1.3 Preoperative Staphylococcal aureus status

5.2.1.3.1 Staphylococcus aureus and SSI risk

Preoperative Staphylococcus aureus carriage was found to be an independent risk factor for surgical site infection following multivariate analysis in Study 2 (OR 1.9, 95% CI 1.01 – 3.52). This is an important finding for two reasons; firstly, it was the only modifiable risk factor identified from the analysis, and secondly, although there is compelling evidence supporting this relationship in adult surgical populations (Bode et al, 2010), this positive relationship has not previously been demonstrated within a paediatric surgical population.

This finding is not consistent with recently reported studies. Macher et al (2017) in a single-centre study of 68 infants (mean age 2.8 months) after cardiac surgery found no association between Staphylococcus aureus carriage and SSI after adjusting for age and operation complexity (OR 1.03, 95% CI 0.22 – 4.82). Similarly, Silvetti et al (2017) studied methicillin-resistant Staphylococcus aureus (MRSA) carriage in 158 paediatric patients prior to cardiac surgery, again finding no association between carriers and non-carriers with the incidence of sternal wound infection (11.9% vs 9.4% respectively). Of note, in addition to low sample sizes, both of these studies had methodological limitations – duration of follow-up in Macher et al (2017) was two weeks after surgery, and Silvetti et al (2017) used a definition for sternal wound infection as a 'localized condition resulting from infectious agents and toxins',

suggesting a diagnostic requirement for positive microbiology. Both factors may have reduced overall SSI incidence and introduced the possibility of a Type 1 error.

5.2.1.3.2 Rate of Staphylococcus aureus carriage

Findings from the large retrospective audit demonstrated an overall paediatric Staphylococcus aureus carriage rate of 20% (119 positive results out of 605 children screened preoperatively). Only one infant was MRSA positive. These findings appear to be consistent with carriage rates reported in the literature for the general population (Lebon et al, 2008). Reported rates from paediatric studies also support this finding, with Macher et al (2017) reporting a carriage rate of 26.5%, and Steiner et al (2014) reporting 20.2%. Findings from the case study demonstrated a neonatal carriage rate of 8%, with only one patient being positive out of the 13 neonates screened. Data are consistent with the findings of Jimenez-Turque et al (2012) who reported a 9.3% incidence of colonization at birth in healthy neonates. Chatzakis et al (2011) has also demonstrated peak colonization occurs in infancy, with the mode of transmission favoring close-contact rather than vertical transmission. Taken together, these results would support the lower rates of neonatal Staphylococcus aureus carriage which have been observed, as a requirement for hospitalization is a factor which will likely alter patterns of close-contact transmission in mothers who are persistent carriers. In addition, the low rate of preoperative breastfeeding reported in the case study would likely reduce the probability of transmission by close-contact further.

As Staphylococcus aureus is a major pathogen in both community-acquired and nosocomial infections these findings are important. In addition to the identified rates of carriage in the population under study, there is an additional potential risk of environmental Staphylococcus aureus transmission whilst hospitalized for surgery. This risk has previously been observed in a Swedish neonatal unit where transmission from maternity staff to neonates was identified (Merrelius et al, 2013). Although during the active periods of data collection for this research study point-prevalence observations regarding hand hygiene episodes suggest compliance with infection-control practices which should mitigate against the risk of hospital acquired Staphylococcal infection (Matussek et al, 2007), additional known risk factors for Staphylococcus aureus colonization are indwelling venous access catheters, antibiotic therapy and requirement for ventilation (Kim et al, 2007), all of which were necessary in the surgical population under study.

Taken together these findings are important because they suggest that having a positive carriage status preoperatively remains an independent risk factor for SSI irrespective of the existing preoperative decolonization practices, supporting both the potential risk for horizontal

recolonization from family members in addition to the risk from hospital environmental colonization. By extending the period of decolonization for the duration of hospital stay, or until all surgical wounds have healed, may be an appropriate risk reduction strategy.

5.2.1.4 Length of stay

Findings from this study revealed a trend towards longer hospital length of stays and increasing incidence of infection. It is not possible, however, to determine whether this is causal or an effect. Although in the case study shorter hospital stays were linked with poor wound healing and superficial surgical site infection, longer lengths of stay appeared to be associated with more significant infection and other postoperative morbidity. Whether postoperative infection was the cause or the result of longer lengths of stay is challenging to attempt to unravel, and far beyond the remit of this research project, but multiple complications appeared to co-exist in those patients with increasing lengths of stay.

There is support for this in the literature, with Richards et al (1999) reporting incidence of nosocomial infection in U.S. paediatric intensive care units to be strongly correlated with length of stay, central venous lines and mechanical ventilation. Furthermore, Brown et al (2003) studied 355 children after heart surgery to identify risk factors for prolonged length of stay. Following multiple regression analysis, preoperative factors were identified as preoperative mechanical ventilation, neonatal status and the presence of two or more medical problems. Postoperatively, sepsis was identified as a risk factor with a reported incidence of 9%, with the risk of a septic episode increasing with increasing length of stay and approaching 50% at 30 days. Of interest, they identified a small number of patients experienced a cluster of complications and accounted for a 'domino effect' in terms of length of stay (that is, the longer the length of stay, the greater the risk of complications including sepsis). A similar finding was reported by Johnson et al (2016) reporting a median length of postoperative stay as 6 days (IQR 4 – 11 days) but noted 10% of patients had stays longer than 26 days, and 5% with stays longer than 51.

Therefore, prompt management of other non-infection related postoperative complications, thereby reducing length of intensive care stay, may be an important factor when trying to implement infection-reduction strategies. This hypothesis suggested by Brown et al (2003) appears to be consistent with the study findings in that increased length of stays appeared to be associated with more episodes of postoperative complications and occurred in tandem with greater disruption to enteral feeding, although this disruption did not necessarily result in significant weight loss.

Within a surgical specialty now experiencing low operative mortality, postoperative length of stay is increasingly being reported as a marker of morbidity (Agarwal et al, 2014; Sinzobahamvya et al, 2013). Associations between specific complications and length of stay, however, are not well defined (Johnson et al, 2016) with prolonged hospital length of stay typically being associated with other associated comorbid conditions (Saharan et al, 2014). However, continued exposure to the hospital environment - particularly following surgery when the body's first line defence against infection has been breached by surgical incision, indwelling venous lines and drains - may act as a co-factor in the development of postoperative infection (perhaps except for superficial SSI which may be a relatively minor infection complication when compared to other infective and non-infective complications, rarely necessitating continued inpatient stays). Such co-factors may exist which independently may be relatively mild when experienced in isolation, but when coupled with other risk factors might exponentially affect morbidity. Although an interesting hypothesis, this could not be determined from this research study.

However, the research findings do introduce the possibility of competing risk – that is, when neonates are exposed to several postoperative complications the occurrence of one may remove the other from being observed (Lai et al, 2017; Ha et al, 2016). To illustrate this point, in Study 3 superficial wound related complications were seen in neonates with the shortest lengths of stay, who received no further antibiotic therapy beyond initial surgical prophylaxis. With chest closure in these short-stay neonates occurring on the day or within 24 hours of surgery, no additional antibiotics were administered during the remaining hospital stay. Conversely, for those long-stay neonates who received prolonged antibiotic therapy for other infection-related complications, this may have had a secondary protective effect against SSI development and prevented it from occurring – in other words, in this competing-risks setting, significant infection which is associated with additional antibiotic therapy removes the likelihood of superficial SSI from occurring. In study one, neonates were underrepresented in the research and excluded from the largest study reporting SSI as an outcome. In study two, SSI was the only infection complication considered and additional postoperative infection complication or antibiotic therapy was not reported but neonatal length of stay was considerably shorter than that reported in the case study, with a duration more reflective of those neonates with minimally interrupted feeding patterns in Study 3. A competing risk hypothesis would explain the finding of higher rates for superficial SSI in the retrospective cohort study due to fewer or no postoperative complications requiring additional antibiotic administration, reflected by the shorter lengths of hospital stay.

Although purely hypothetical, there is an important clinical and quality question raised – both length of stay and SSI rates are outcomes which are increasingly being viewed as important quality indicators (PHE, 2011;), but a competing risk hypothesis would suggest that low superficial SSI rates may in fact be a consequence of more severe types of postoperative infection complications occurring which require additional antibiotic therapy, such as bloodstream infection and pneumonia, especially when associated with an increased length of hospital stay. This appears consistent with data from both the retrospective cohort and the case study, where those with superficial SSI had hospital length of stays shorter than those without superficial SSI but with other infection complications.

5.2.1.4 Competing risk

A theory of competing risk was generated through the analysis of the case study, where it was apparent that rates of SSI appeared lower than those reported in the cohort study, but average length of postoperative stay was longer. Significant non-SSI infection complications appeared to predominate accounting for this extended length of stay, especially apparent with the ongoing requirement for intensive care. As treatment for any early postoperative infection is intravenous antibiotics, it is therefore biologically plausible that the additional antibiotic therapy administered to the longer stay neonates in the case study could have provided protection against the development of SSI. As non-SSI infection and additional antibiotic use was not accounted for within the cohort study, it is also feasible that the protective effect which was observed between low weight-for-age and SSI in the cohort study may in fact have been confounded by additional antibiotic administration which was unmeasured, and that the latter explains the unexpected observed relationship. The implication of this is that current SSI surveillance methodology, carried out in isolation from either the surveillance of all postoperative infection or additional antibiotic use, may in fact be misleading and result in erroneous conclusions about the quality of surgical care.

5.2.2 The relationship between WAZ, cardiac children and infection

Malnutrition, as classified by low weight-for-age z-scores, was not found to be a risk factor for surgical site infection. On multivariate modelling, having a cardiac diagnosis requiring surgery during early childhood and being in an underweight WAZ category appeared to be protective for SSI until reaching school-age, when the odds of infection equalized between the underweight and normal/overweight groups. At this age, surgery is most likely performed for obstructive heart lesions rather than heart failure caused by increased pulmonary blood flow which are the most often associated with faltering growth, which are most commonly operated on in early infancy.

Study findings demonstrate that the incidence of low birth weight in association with a congenital heart disease diagnosis was low, and neonates were generally within a normal WAZ category at birth and time of surgery. Despite Mendelian and chromosomal syndromes accounting for approximately 20% of children with congenital heart disease, and which are known to result in growth disturbances (Medoff-Cooper & Ravishankar, 2013), there was a low incidence of associated abnormalities within the study populations included in this study.

There is mixed evidence on whether babies born with congenital heart malformations are of low birth weight. Rosenthal et al (1996), Kramer et al (1990), Jacobs et al (2003) and Petrossian et al (2015) have all reported an association between low birth weight and congenital heart disease. Only babies born with transposition of the great arteries (TGA) were found to be of similar weight to their normal counterparts (Petrossian et al, 2015). However, these studies were based on data from over 20 years ago, and results of this study are in keeping with more recent evidence that cardiac babies are born of normal, or near normal weight, and that low weight as indicated by WAZ scores <-2 SDs is a phenomenon seen during infancy rather than the neonatal period (Anderson et al, 2011; Mitting et al, 2015; Li et al, 2017; Ross et al, 2017). Perhaps in the intervening years since these early studies were published better antenatal diagnosis has altered patterns of prenatal care which has had a positive outcome on weight at birth, for example, health promotion strategies to reduce alcohol consumption and smoking during pregnancy. Consequently, although age remained strongly related to postoperative outcomes including infection, this is not so clearly associated with low body weight.

5.2.3 Definitional inconsistencies of nutritional status and infection in existing literature

This research identified the plethora of definitions currently in use to classify both undernutrition and infection-related complications. The lack of robust and universally agreed definitions – in either research or clinical practice – has made the answering of the original research question challenging and accounted for a major cause of the low-quality evidence currently available.

WAZ was chosen as it has been linked with both short and long-term outcomes following neonatal cardiac surgery in recent study, finding associations with late death (Eskedel et al, 2008; Mitting et al, 2015); increased durations of mechanical ventilation (Mitting et al, 2015; Saharan et al, 2015); length of stay and hospital readmission (Saharan et al (2015). Despite recent evidence that nutrition and growth in hospitalized children remains poor (Pichler et al, 2014), there continues to be a focus on weight-based anthropometry in clinical areas. Height assessment occurred in the study populations as a requirement prior to bypass surgery, but

this was not reassessed at hospital discharge irrespective of length of hospital stay. Adequacy of postoperative growth, therefore, was assessed on nutritional intake and subsequent increases in weight, under the watchful eye of clinically-based dieticians. Although nutritional risk scores have been applied and validated for hospitalized children outside of an intensive care setting (Secker et al, 2007; Hulst et al, 2010; Pichler et al, 2014), paediatric intensive care specific nutrition risk scores are sadly lacking but desperately needed when children are known to be at most nutritional risk (Martinez & Mehta, 2016).

Findings have demonstrated a distinct lack of consistency in terminology and of robust definitions with which to reliably determine the existence of undernutrition as an exposure of research interest. A similar observation was made for the classification of postoperative infection complications, where lack of a standardized and universally applied definition makes extrapolating results from previous studies fraught with difficulty, and therefore attempting to identify the true incidence of either undernutrition or healthcare acquired infection in a surgical population is challenging. The lack of standardized nomenclature and reporting methodology with which to classify postoperative complications has previously been identified by Costello et al (2012) as making precise estimates of incidence limited, making the identification of potential causal links which might highlight areas for potential risk modification difficult.

This varying methodology made it difficult to interpret the significance of the high SSI rates reported within the study, as there are no directly comparable studies with which to inform the true incidence. Additionally, methodological limitations within this research study may have erroneously resulted in a falsely elevated reported incidence of SSI. These factors highlight the extreme importance of standardized definitions, along with the need for risk adjusted reporting especially in relation to patient age which appears to have a significant impact on incidence.

5.3 Original contribution to knowledge

The key contributions to knowledge from this study will now be summarized. Are summarized below. Plans for their future dissemination can be found in Appendix 17.

1. A competing risk hypothesis would suggest the current focus on SSI rate as an indicator of the quality of care may be misleading, as findings suggest the existence of more serious infection and additional antibiotic use is protective against superficial SSI. Therefore, consideration needs to be given to the reporting of all postoperative infection rather than SSI in isolation.

2. Undernutrition, as defined by WAZ scores <-2SDs, was not found to be a risk factor for development of SSI. In contrast, having a cardiac diagnosis requiring surgery during early childhood and being in an underweight WAZ category appeared protective against SSI until school-age is reached, when risk equalizes.
3. Cardiac neonates do not have the opportunity to develop illness-related weight loss prior to surgery; most in both Study 2 and Study 3 were of normal birth weight. This contrasts with previously published research which report cardiac babies to be small for age. Low weight-for-age is greatest in the infant population prior to surgical repair, as identified from Study 2.
4. A positive Staphylococcal aureus status prior to surgery in Study 2 was identified as an independent risk factor for surgical site infection in children after cardiac surgery. This is the first study in a pediatric cardiac surgical population which provides evidence for not only preoperative MSSA eradication, but ongoing suppression until surgical wounds have healed.
5. Reducing hospital length of stay may be a key modifiable factor in reducing infection risk. Although infection in this surgical cohort was multifactorial, there was an association seen between increased length of stay and risk of healthcare-associated infection. Neonatal length of stay in all clinical areas (operating room, intensive care and ward environments) are greater than for older children. Whether this is directly causal or related to an unmeasured confounding variable (i.e. infection acts as an independent rather than dependent variable) warrants further exploration.

5.4 Strengths of the study

This study has confirmed infection complications in children following cardiac surgery is a multifactorial phenomenon, reflecting the previous reports from within adult surgical populations, particularly with respect to surgical site infection. Using a variety of observational methodology, the relationship between postoperative infection and undernutrition was investigated, and although these have both been reported separately, few good-quality studies existed which looked at them in combination.

This study included a complex neonatal surgical population previously excluded from research and has identified novel patterns of SSI risk, and emphasized the importance of early postoperative factors in the aetiology of SSI. The suggestion that early patterns of feeding can predict surgical morbidity is a novel finding which warrants further exploration.

The research followed a methodical approach which utilized independent but related observational studies in order to identify preoperative risk factors for SSI. Findings identified three independent patient and operative risk factors for infection, with only one being open to modification prior to surgery. The stages of independent study were developed from preceding study findings, therefore evolved through data patterns identified. The integration of findings from all three independent studies support the knowledge claims.

Following a systematic review which reinforced the relevance of the research question, the infection outcomes in both observational studies were already known and had been validated either before the start of the study, or prior to data analysis. Therefore, the chance of reporting bias in the diagnosis of infection-related outcomes was not an issue.

As causal associations are not possible with observational methodology, biological plausibility was considered in the interpretation of both variables and findings, and the researcher-practitioner role enabled a degree of clinical expertise to be utilized in this interpretation.

5.5 Limitations of study

Some potential limitations are outlined below:

This is a single-site study in a highly specialized paediatric surgical population, therefore the applicability of findings to other surgical specialties and other settings may be limited.

As a practitioner-researcher, there was the awareness that preconceptions, previous experiences, clinical expertise and personal beliefs might influence and potentially bias aspects of the observational research process. Whilst other forms of research methods were considered, this awareness ultimately influenced the final choice of study method. It is recognized that methods targeting clinician and parent opinion might have contributed to a deeper understanding of the relationship and significance of what is a multifactorial phenomenon, and that further insights might have resulted. As such, researcher bias will remain as a limitation, despite the use of strategies to minimize this risk, such as the use of the wider research team and expert colleagues, and the utilization of a multi-staged research approach.

As with any research study occurring over an extended period of time, there have been practice and organizational changes which have been beyond the control of the researcher. Changes in the consultant surgical team and the appointment of additional intensive care consultants may have altered aspects of surgical and postoperative management, which in turn may have altered clinical outcomes such as length of stay. Changing complexity of the

paediatric cardiac surgical population may also have contributed to findings, along with a lower threshold for postoperative extracorporeal support with recognized regional ECMO provision. In addition, a move to a new hospital environment will undoubtedly have led to variations in how children are cared for. Although these changes did not occur during active data collection periods for each independent study, it must be recognized that some may account for changes identified in neonatal length of stay identified between Studies 2 and 3.

Weight-for-age z-score categories were utilized rather than absolute scores in both study two and study three. This meant only absolute changes in z-score were identified, rather than within category trends. This may have reduced the sensitivity of the studies to detect faltering growth.

As with any observational study, a cause-and-effect relationship between independent risk factors and outcome cannot be claimed. Unmeasured or unknown confounding variables may account for the associations found. In addition, measurement error in recorded height and weight measurements may have potentially resulted in misclassification of nutritional status. The use of a highly sensitive SSI surveillance methodology may have overestimated the true rate of superficial SSI.

Finally, without research funding and with the time restrictions imposed during a formal research programme, aspects of the study were bespoke in order to address these restrictions. For example, whereas a prospective cohort study would have been the preferred methodology for Study 3, it was appreciated that the time needed to ensure an adequate neonatal sample size would not be a feasible study method for the remaining period of study.

5.6 Recommendations/implications for further research

Firstly, definitions for all infection-related complications need to be robustly defined and consistently applied across future studies looking at postoperative outcome. This research has identified both methodological variation between different criteria for defining surgical site infection and, perhaps more importantly, that measuring superficial SSI in isolation from other infection-related complications may not be as reliable an indicator of quality care as has previously been inferred. The competing-risk hypothesis that has emerged from this research suggests that high superficial rates of SSI may in fact be representative of better surgical outcome – that is, it occurs only when the rate of more serious infection-related complications (necessitating longer durations of antibiotic therapy and additional length of stays) do not. Shifting the focus away from reporting SSI to reporting all infection-related complications and antibiotic use will require a climate change and the willingness to, or the necessity of,

reporting such surgical morbidity, with the robust definitions needed to ensure consistency ad meaningful interpretation.

Secondly, there is a need for large, adequately powered prospective studies using a standardized method of nutritional assessment and agreed definitions for undernutrition. Without this, determining the precise relationship between nutritional status and the true impact on clinical outcomes will be impossible to determine. Consideration should be given to using alternative methods to weight-based data to assess nutritional status, the favoured technique in those studies meeting criteria for inclusion in the systematic review.

Despite the recognized importance of measuring and plotting child development and growth, the interpretive value of these data in clinical practice may be inadequate. There is agreement in the literature that despite recognition that malnutrition is important, and a regularly observed phenomenon in hospitalized children with chronic conditions, there is poor integration of this knowledge into clinical practice (Hartman et al, 2012; Wisken et al, 2012) and little research focuses on its relationship with outcome.

Better nutritional assessment methodology is required. Current evidence indicates that biomarkers are unhelpful primarily due to the effect surgical stress has on acute phase proteins, for example albumin, which has been one of the most frequently used markers for the assessment of nutritional status. The enteral feeding interruption patterns emerging from Study 3, for example, may be predictive of longer-term nutritional outcome and this warrants further exploration.

The finding that methicillin-sensitive Staphylococcus aureus (MSSA) carriage remained associated with increased risk of healthcare-associated infection was surprising, particularly in a unit with a preoperative MSSA screening and decolonization guideline prior to cardiac surgery. This raises important questions regarding compliance, identified as being sub-optimal during Stage 3, but also in terms of duration adequacy and in particular, potential patterns of recolonization whilst children remain in hospital. The role of continued anti-microbial washing until full wound healing is of particular interest in terms of post-discharge wound healing complications.

5.6 Recommendations for clinical practice

SSI surveillance methodology

Objective, MDT approach to the identification and classification of SSI is needed, as advocated by PHE, with engagement from stakeholders involved in the care of children

after paediatric cardiac surgery. This needs to be adapted to be paediatric specific. This will promote engagement with Paediatric Cardiac Surgeons, and with sufficiently robust definitions that can be universally applied for the mandatory reporting of surgical site infection, as advocated by NICOR (Franklin et al, 2017).

MSSA eradication

A positive status was an independent risk factor for SSI on multivariate analysis. Although compliance monitoring of preoperative MSSA screening and decolonization was not part of this study, results show that there is room for improvement. In view of findings, there is evidence to suggest extended suppression after surgery whilst the wound is in the early stages of healing may be of some benefit and is one factor identified that remains modifiable.

Feeding algorithms

Missed opportunities to optimize enteral feeding, even in the presence of fluid restrictions in place on intensive care, exist. The reduction of unnecessary pre-procedural starvation, early trophic feeding, utilisng temporary feed increases to compensate for necessary missed volumes, and in particular the reevaluation of existing post-cardiac surgical fluid allowances are modifiable factors during the postoperative period that would improve nutritional outcomes for children following paediatric cardiac surgery.

Strategies to reduce length of stay

The evidence suggests that aggressive early identification and management of postoperative morbidity in children failing to progress after surgery would be of benefit in reducing the ongoing risk of healthcare-associated infection occurring as a consequence of protracted intensive care stay. Polito et al (2011) has identified cardiac reintervention as being the strongest predictor for prolonged mechanical ventilation (OR 14.8, 95% CI, 3.6 – 60.6, $p < 0.001$), therefore when coupled with the findings from this research, a potential reduction in intensive care stay by adopting an early reintervention strategy could benefit nutritional outcomes. Although most unplanned reinterventions may not be modifiable, the adoption of an early reintervention strategy is, and evidence exists to suggest it would lead to both improved surgical morbidity and nutritional outcomes for children after paediatric cardiac surgery.

5.8 Recommendations for policy

The current focus of both national and international audit following paediatric cardiac surgery remains on 30-day mortality rates (NICOR; EACTS; STS). In a surgical population where survival rates have dramatically improved even in the most complicated neonatal surgery, this focus should now shift in the direction of morbidity outcome and try to establish how children are surviving. Findings of this study support the need for additional audit metrics which focus beyond this initial 30-day period, and may be a better marker of operative success, and act as a stimulus for future quality improvement.

In addition, as current methods of SSI surveillance do not consider the potential impact of co-existing infection, the findings of this study suggest that SSI incidence reported in isolation from other infection complications may not be a sufficiently robust indicator of the quality of care. Antibiotic use for other infection may be exerting a protective effect on the incidence of superficial SSI, which one could then hypothesize as superficial SSI in children being a potential marker of good surgical outcome.

Finally, in view of the high risk of surgical neonates, there is a need highlighted for any additional postoperative outcome reporting to be age-stratified, with incidence reported per defined denominator data.

5.9 Conclusion

Little evidence was found with respect to the identification of independent predictors with which to guide and define practice in terms of infection risk reduction. However, both nutritional status and length of stay appear to be implicated as important factors associated with infection related outcomes, although their precise relationship remains to be defined.

This research provides further evidence that causes of postoperative infection complications following paediatric cardiac surgery are multi-factorial in aetiology and suggests they cannot be considered in isolation from other postoperative complications. It also confirms the poor reliability and varied practice regarding nutritional assessment methodology, which until addressed will make further progress in this area challenging.

However, reported feeding outcomes at time of hospital discharge for neonates experiencing short postoperative stays following uncomplicated complex neonatal cardiac surgery were favourable in comparison to previously published studies, but confirms there remains opportunity for improved feeding practices in intensive care environments when longer stays are experienced, which if addressed may be found to have potentially protective effects in

neonates who remain at the highest risk of postoperative infection complications. The hypothesis of competing risk generated through this research raises the question regarding the current validity of using SSI surveillance as a marker of surgical performance.

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Appendices

Appendix 1: Database search strategy (Systematic review)

1a: MEDLINE via OVID

Performed on 09/05/14

1. nutrition assessment/
2. nutritional status/
3. nutrition disorders/
4. exp *malnutrition/
5. *anthropometry/
6. (nutrition$ and (assess$ or status or disorder$)).mp.
7. "subjective global assessment".mp.
8. undernutrition.mp.
9. malnutrition.mp.
10. or/1-9
11. Neonat$.tw.
12. Pediat$.tw.
13. Paediat$.tw.
14. Teenage$.tw.
15. Infant, newborn/
16. Infant/
17. Child, preschool/
18. Child/
19. Adolescent/
20. or/11-19
21. Postoperative complications/
22. *Surgical wound infection/
23. *mediastinitis/
24. exp *endocarditis/
25. (Surg$ and (infect$ or sepsis or septic$)).tw.
26. (Surg$ and (outcome$ or morbid$ or complicat$)).tw.
27. ((Postop$ or post-op$) and (infect$ or sepsis or septic$)).tw.
28. ((Postop$ or post-op$) and (outcome$ or morbid$ or complicat$)).tw.
29. or/21-28
30. 10 and 20 and 29
31. incidence.sh. or exp mortality/ or follow-up studies.sh. or prognos:.tw. or predict:.tw. or course:.tw.
32. 30 and 31

1b: EMBASE with filter via OVID

Performed on 26/03/14

1. nutritional assessment/
2. nutritional status/
3. malnutrition/
4. nutritional disorder/
5. exp nutritional deficiency/
6. anthropometry/
7. child nutrition/
8. infant nutrition/
9. (Nutrition* and (assess* or status or disorder)).tw.
10. (nutrition* or malnutrition or malnourish* or under-nourish* or undernourish* or undernutrition).tw.
11. Subjective global assessment.mp.
12. or/1-11
13. infant/
14. newborn/
15. baby/
16. child/
17. preschool child/
18. school child/
19. adolescent/
20. Neonat*.mp.
21. Babies.mp.
22. Paediatr*.mp.
23. Pediatr*.mp.
24. Teenage*.mp.
25. or/13-24
26. exp surgical infection/
27. exp postoperative infection/
28. exp *wound infection/
29. exp *mediastinitis/
30. exp *endocarditis/
31. Surgical site infection.mp.
32. (postop* and (infect* or sepsis or septic*)).tw.
33. (post-op* and (infect* or sepsis or septic*)).tw.
34. or/26-33
35. exp disease course/ or risk*.mp. or diagnos*.mp. or follow-up.mp. or ep.fs. or outcome.tw.
36. 12 and 25 and 34
37. 35 and 36

1c: CINAHL via EBSCO Host

Performed on 28/04/14

1. (MM "Infant, Newborn+")
2. (MM "Child, Hospitalized")
3. (MM "Adolescent, Hospitalized")
4. (MM "Infant, Hospitalized")
5. (MM "Child, Preschool")
6. S1 OR S2 OR S3 OR S4 OR S5
7. (MH "Malnutrition")
8. (MM "Nutrition Disorders+")
9. (MM "Body Weights and Measures+")
10. (MM "Nutritional Status")
11. (MM "Nutritional Assessment")
12. (MM "Nutritional Assessment")
13. AB nutrition* AND TX ((assess* or status or disorder))
14. TX malnutrition
15. subjective global assessment
16. malnutrition OR nutrition* OR under?nutrition OR under?nourish* OR malnourish*
17. S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
18. (MH "Infection+")
19. (MM "Mediastinitis")
20. (MH "Endocarditis+")
21. (MH "Bacterial Infections+")
22. (MH "Postoperative Complications+")
23. AB complication* AND TX infect* OR TX septic*
24. TX surgical site infection
25. infect*
26. postoperative AND (sepsis or septic*)
27. surgical N2 infect*
28. TX postoperati* AND (sepsis OR septic* OR infect*)
29. TX surgical N1 ("site infection" OR infect*)
30. S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 OR S29
31. S6 AND S17 AND S30

Appendix 2: Data extraction form (Systematic review)

Study Characteristics

	Descriptions as stated in report/paper		Location in text or source *(pg & ¶/fig/table/other)*
Objectives of study *(e.g. incidence, prognosis, exploratory)*			
Design *(e.g. Cohort, Case Control, NRCT)*	Retrospective / Prospective		
Setting *(include country, hospital setting from where prticipants were enrolled)*	Single site / multiple site		
Start date			
End date			
Total no. participants (cohort/series) with no. in each group (case control)? *(or total pop. at start of study)*			
Method of patient selection/recruitment*(e.g inpatient, mail, clinic)*	Yes/No/Unclear		
Duration of participation (from recruitement to last follow-up)			
Confounding variables stated (please list)	None stated		
Withdrawals & exclusions accounted for?	Yes / No / Not applicable		
Ethical approval needed/ obtained for study	Yes No Unclear	Details:	
Informed consent obtained	Yes / No / Unclear		
Notes:			

Participant characteristics

	Description	Location in text or source *(pg & ¶/fig/table/other)*
Population description *(from which population are participants drawn)*		
Type of paediatric surgery		
Study inclusion criteria		
Study exclusion criteria		
Age range *(med; mean if stated)*		
Sex (M/F)		
Weight *(include BMI if stated)*		
Severity/risk of operation *(if stated)*		
Length of surgery *(if stated)*		
Co-morbidities *(please list)*		
Other relevant sociodemographics		
Additional notes/descriptive statistics:		

Exposure (Predictor variable)

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Exposure name *(i.e. malnutrition, undernutrition; poor nutrition)*		
Description of category of nutritional assessment/status *(include tool/classification/cutoffs used where provided)*		

If nutritional assessment tool used, is it validated/recognised?	Yes / No / Unclear	
Method of exposure measurement *(e.g. anthropometric, biochemical test)*		
Timing of nutritional assessment *(e.g. pre-assessment, pre-operative, post-operative)*		
Assessor of preoperative nutritional assessment *(i.e. who made the exposure assessment)*	Not stated Medical records Independent assessor Clinician treating child Researcher Other Unclear	
Co-interventions *(if any)*		
Other risk factors (confounders) adjusted for in analysis *(please list)*		
Notes:		

Outcomes (copy and paste table for each relevant outcome)

	Description as stated in report/paper	Location in text or source *(pg. & ¶/fig/table/other)*
Outcomes relevant to the review	Blood stream infection Surgical site infection – total, wound, Mediastinitis, Endocarditis Pneumonia/chest infection Length of hospital stay Mortality Other infection *(please state)*	
Time points for outcome measurement? *(specify duration of follow-up for both groups)*		
How was outcome data collected? *(please circle)*	Not stated / medical notes / postal questionnaire / telephone appointment / routine follow up appointment / study appointment / other	

How was infection outcome data defined? *(e.g. diagnostic criteria/classification if provided)*	Clear/ Unclear	
Was the person collecting outcome data blinded to exposure group?	Yes / No / Unclear	
Is outcome/tool validated/recognised?	Yes / No / Unclear	
Additional notes:		

Other

Study funding sources *(including role of funders)*		
Possible conflicts of interest *(for study authors)*		
Notes:		

Appendix 3: Quality Assessment (Systematic review)

Newcastle-Ottawa Quality Assessment Scale: **Cohort Studies**

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort is:
   a) truly representative of the average pediatric surgical population of interest*
   b) somewhat representative of the average paediatric surgical population of interest*
   c) a selected group of paediatric surgical patients
   d) not described.
2) Selection of the non exposed cohort is:
   a) drawn from the same population as the exposed cohort*
   b) drawn from a different source
   c) not described.
3) Ascertainment of exposure is:
   a) by secure record (eg surgical records)*
   b) by structured interview*
   c) by written self report
   d) not described.
4) Demonstration that outcome of interest (infection) was not present at start of study
   a) Yes*
   b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) Study controls for _____(most important factor)*
   b) Study controls for additional factors of _____*
   c) No / Unclear

Outcome

1) Assessment of outcome
   a) Independent blind assessment*
   b) Record linkage*
   c) Self report
   d) No description
2) Was follow-up long enough for outcomes to occur
   a) Yes, if median duration of follow-up >= 30 post-op days*
   b) No, if median duration of follow-up <= 30 post-op days or not stated for non-exposed group
3) Adequacy of follow up of cohorts
   a) Complete follow up - all subjects accounted for*
   b) Subjects lost to follow up unlikely to introduce bias - small number lost <= 20% to follow up, or description provided of those lost)*
   c) Follow up rate < 80% and no description of those lost
   d) No statement

Newcastle-Ottawa Quality Assessment Scale: **Case Control Studies**

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) Yes, with independent validation*
   b) Yes, eg record linkage or based on self reports
   c) No description
2) Representativeness of the cases
   a) Consecutive or obviously representative series of cases*
   b) Potential for selection biases or not stated
3) Selection of Controls
   a) Same surgery controls without outcome*
   b) Other surgery controls
   c) No description
4) Definition of Controls
   a) No history of outcome*
   b) No description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) Study controls for _____*
   b) Study controls for additional factors of _____*
   c) No / Unclear

Exposure

1) Ascertainment of exposure
   a) Secure record (e.g. surgical records)*
   b) Structured interview where blind to case/control status*
   c) Interview not blinded to case/control status
   d) Written self-report or medical record only
   e) No description
2) Same method of ascertainment for cases and controls
   a) Yes *****
   b) No
3) Non-Response rate
   a) Same rate for both groups*
   b) Non respondents described
   c) Rate different and no designation

Appendix 4: Outcome data extraction form (Systematic review)

Copy and paste the appropriate table for each outcome of interest, including subgroups if relevant.

Dichotomous outcomes (e.g. infection, mortality)

	Description as stated in report/paper				Location in text or source *(pg. & ¶/fig/table/other)*
Outcome description					
Time point measured *(specify from time of surgery if possible)*					
Unit of measurement *(e.g. patients,operations)*					
Results Reported / Estimated		Exposed (Malnourished)	Not exposed (Eutrophic)	Totals	
	No. with outcome				
	No. without outcome				
	Totals				
Any other results calculated from raw data?	RR = Unadjusted CI =				
Any other results reported? *(e.g. odds ratio, risk difference, CI or p value, regression coefficient)*	Yes / No				
Missing participants/data accounted for? *(include reasons missing)*	Yes / No / Unclear / Not applicable		Yes / No / Unclear / Not applicable		
Statistical methods used in the study *(e.g. Multiple logistic regression)*					
Additional notes:					

Continuous outcomes (e.g. length of stay)

	Description as stated in report/paper						Location in text or source *(pg. & ¶/fig/table/other)*
Outcome description							
Time point measured *(specify from time of surgery if possible)*							
Results	Exposed (n=)			Not exposed (n=)			
	Mean	SD *(or other variance, specify)*	No. participants	Mean	SD *(or other variance, specify)*	No. participants	
Any other results reported *(e.g. mean difference, CI, p value, correlation coefficients)*							
Missing participants/data accounted for?							
Reasons missing							
Statistical methods used *(e.g. Multiple linear regression)*							
Additional notes: (include other information relevant to the results. If results were estimated from graphs or calculated from raw data using a formula, state and provide the formula here. Any calculated results must be explicit here)							

Other information

	Description as stated in report/paper	Location in text or source *(pg. & ¶/fig/table/other)*
Key conclusions of study authors		
References to unpublished data?	Yes / No	

Correspondence required for further study information *(from whom, what and when)*	
Additional notes:	
References to other relevant studies: (*Please check all references for potential inclusion suitability and list article below)*	

First Author	Journal/Conference	Year of Publication

Appendix 5: Study Characteristics (Systematic review)

5a: Characteristics of included studies

Study ID: Al Bassam 1994		
Aim of study	To evaluate the prevalence of protein calorie malnutrition and the correlation of preoperative nutritional status with postoperative morbidity and mortality; to study the predictive value of nutritional variables in detecting postoperative morbidity	
Methods	**Design** **Duration** **No of centres** **Country (City)**	Prospective cohort study 18 months, dates not provided Single Saudi Arabia
Participants	**Participants** **Age** **Gender** **Ethnicity** **Inclusion criteria** **Exclusion criteria** **Co-morbidities**	62 paediatric patients undergoing major and intermediate general surgical procedures Mean 4.1 years (range 37 days – 15 yrs) 38 male; 24 female Not reported Not defined Not defined Not reported
Definition of exposure	**Definition** **Description/classification**	Protein calorie malnutrition Weight for height <90% standard, weight for age <95% standard (NCHS growth charts) Triceps skin-fold <35% standard (Frisancho 1974) Serum albumin 0-5yr <3; 6-12yr <3.5 Hb 1-3yr <10; 3-6yr<11; 6-12yr 11.5
Outcomes relevant to the review	**Definition** **Description/classification** **Study incidence of outcome** **Unit of analysis**	Pneumonia Pneumonia= clinical signs and symptoms with radiological changes on chest xray 6.75% Operation n= 74
Notes	Overall incidence of malnutrition in study population was 59% Funding issues/conflict of interest issues were not declared Small population for study duration, with inadequate information to assess adequacy of selection criteria therefore at risk of bias	

Study ID: Anderson 2011		
Aim of study	To identify specific anthropometric and cardiovascular variables predicting lower weight for age Z scores and poorer short term surgical outcomes at operation (Completion of Fontan).	
Methods	**Design** **Duration** **No of centres** **Country (City)**	Retrospective case series January 2003 to December 2008 Single USA (Cincinnati)
Participants	**Participants** **Age** **Gender** **Ethnicity** **Inclusion criteria** **Exclusion criteria** **Co-morbidities**	55 paediatric patients undergoing cardiac surgery (completion of Fontan) Median 47 months (range 18-71) 27 male; 28 female Not reported Patients undergoing Fontan completion Premature birth <35 weeks gestation; Chromosomal abnormalities; major congenital abnormalities of nervous system, GI system or respiratory system Not reported
Definition of exposure	**Definition** **Description/classification**	Failure to thrive Weight for age z score < -2.0
Outcomes relevant to the review	**Definition** **Description/classification** **Study incidence of outcome**	Infectious complications (combined); postoperative length of stay Pneumonia=culture-positive endotracheal tube aspirate with chest x-ray changes

	Unit of analysis	17% Patient
Notes	Overall incidence of WAZ <-2 in study population = 19% Funding issues/conflict of interest issues were not declared	

Study ID: Bhattacharyya 1990, 1993		
Aim of studies	To determine the incidence of wound infection and other hospital-acquired infections and analyse potential etiologic factors	
Methods	**Design** **Duration** **No of centres** **Country (City)**	Prospective cohort study December 1986 to January 1988 Two USA (New Mexico)
Participants	**Participants** **Age** **Gender** **Ethnicity** **Inclusion criteria** **Exclusion criteria** **Co-morbidities**	608 patients undergoing 676 general operative procedures (mainly gastrointestinal) requiring skin incision 137 neonates; 197 infants; 342 children Male 436; female 240 Not reported Operative procedure requiring general anaesthesia and skin incision Procedures performed on ward or intensive care Presence of "coexisting disease process or anomaly" was collected pre-operatively, but no details were provided
Definition of exposure	**Definition** **Description/classification**	Malnutrition (moderate or severe) Waterlow's weight-for-height
Outcomes	**Definition** **Description/classification** **Study incidence of outcome** **Unit of analysis**	Wound infection and nosocomial infection ASEPSIS score >21 for wound infection; Septicaemia = positive blood culture with sepsis; CLaBSI = positive blood culture without sepsis; Pneumonia = clinical and radiological features; UTI = >10,000 bacteria per mm; intrabdominal abscess = fever, positive CT findings SSI 2.5%; combined other 8.6% Operation n=615
Notes	Overall incidence of malnutrition in study population was 28% Funding issues/conflict of interest issues were not declared 608 patients, undergoing 676 procedures, with 615 nutritional assessments undertaken 53 nosocomial infections reported in 38 patients, with age group provided, but impossible to ascertain nutritional status of those patients having more than one infection for individual breakdown by complication	

Study ID: Farley 2014		
Aim of study	To identify risk factors for the development of deep surgical site infection following spinal surgery	
Methods	**Design** **Duration** **No of centres** **Country (City)**	Retrospective case control study Five year period, dates not reported Single USA (Michigan)
Participants	**Participants** **Age** **Gender** **Ethnicity** **Inclusion criteria** **Exclusion criteria** **Co-morbidities**	Children undergoing scoliosis surgery for spinal fusion, VEPTR lengthening or replacement, growing rod lengthening replacement); Cases = 20, Controls = 50 Average age not reported 21 male, 49 female Not reported Not defined Not defined Not reported
Definition of exposure	**Definition** **Description/classification**	Body Mass Index Underweight = BMI <18.5; Normal = BMI >18.5 to <24.9; Overweight = >25 to <29.9 ; Obese = >30
Outcomes	**Definition**	Delayed deep surgical site infection

relevant to this review	**Description/classification** **Study incidence of outcome** **Unit of analysis**	CDC criteria for SSI; 'delayed' defined as up to 2 years N/A Patient
Notes	Overall incidence of underweight children in the study was 44% Funded by departmental grant, no conflict of interest stated Some young adults included, but individual patient data provided permitting exclusion of individuals >18 yrs of age	

Study ID: Hatlen 2010		
Aim of study	To determine if the presence of poor nutrition and/or positive urinary cultures before elective spinal surgery in children with meningomyelocele increases the risk of spinal infection	
Methods	**Design** **Duration** **No of centres** **Country (City)**	Retrospective cohort study 1974 to 2007 Single USA (Washington)
Participants	**Participants** **Age** **Gender** **Ethnicity** **Inclusion criteria** **Exclusion criteria** **Co-morbidities**	59 children with mylomeningocele undergoing surgery for scoliosis 10 years 6 mths (range 1.8 – 18 yrs) 29 male, 31 female Not stated Children with mylomeningocele who underwent spinal fusion and instrumentation procedures from 1974 - 2007 None stated Not reported
Definition of exposure	**Definition** **Description/classification**	Poor nutritional status Serum albumin level less than 55g/L or a haematocrit (Hct) equal or less than 33.
Outcomes relevant to this review	**Definition** **Description/classification** **Study incidence of outcome** **Unit of analysis**	Major postoperative infection, including wound infection Wound breakdown with purulence, exposed spinal instrumentation or a positive wound culture 41.7% Operation n=84
Notes	Overall incidence of poor nutrition in the study population = 35% Funding issues/conflict of interest – "nothing to declare" Children grouped according to preoperative nutritional status and/or preoperative positive urine culture (defined as >100,000 colony forming units). Only two groups (poor nutritional status and normal nutritional status) were compared for the purpose of this review, due to the potential confounding effect of positive urine cultures.	

Study ID: Leite 1995		
Aim of study	To evaluate poor nutritional status as a risk factor for postoperative complications in children with congenital heart disease	
Methods	**Design** **Duration** **No of centres** **Country (City)**	Prospective cohort study October 1990 - October 1992 Single Brazil (Sao Paolo)
Participants	**Participants** **Age** **Gender** **Ethnicity** **Inclusion criteria** **Exclusion criteria** **Co-morbidities**	50 children undergoing cardiac surgery divided into high risk and low risk operations, 20 'control' children undergoing non-cardiac (hernia) surgery High risk = Median 12mth (3 – 134); Low risk = Median 42mth (3 -140) High risk = 15 male; 15 female; Low risk = 8 male; 12 female Not reported Children admitted for cardiac (hernia) surgery Weight <2500g; central paralysis; immune deficiency; renal/hepatic failure; blood transfusion within 30 days; infection Not reported
Definition of exposure	**Definition** **Description/classification**	Malnutrition Weight/height <10th percentile; arm circumference <5th

		percentile, albumin <3.5g/dl; transferrin <200mg/dl; Prealbumin >19.6mg/dl
Outcomes relevant to this review	**Definition** **Description/classification** **Study incidence of outcome** **Unit of analysis**	Postoperative complications including infection Buzby et al 1998 16% Patient
Notes	Overall incidence of malnutrition in study population was 78% Funding issues – supported by Hoechst do Brasil Behring Diagnostics division Conflict of interest not declared	

Study ID: Nateghian 2004		
Aim of study	To determine rates and risk factors for surgical site infection following paediatric cardiac surgery	
Methods	**Design** **Duration** **No of centres** **Country (City)**	Prospective nested case control study 1 January 1998 to 31 December 2002 Single site Canada (Alberta)
Participants	**Participants** **Age** **Gender** **Ethnicity** **Inclusion criteria** **Exclusion criteria** **Co-morbidities**	38 children undergoing major paediatric cardiac surgery who developed surgical site infection, with 38 matched controls Cases = Mean 2.13yr; Controls = Mean 3.6 yrs Cases = 18 male, 20 female; Controls = 21 male, 17 female Not reported Patients <18 yrs who had open heart surgery developing SSI or controls from the same cohort matched for age; NNIS risk score (duration of surgery, wound classification, ASA physical status score); and year of surgery Not stated Not reported
Definition of exposure	**Definition** **Description/classification**	Failure to thrive Weight <2 standard deviations below the norm for age
Outcomes	**Definition** **Description/classification** **Study incidence of outcome** **Unit of analysis**	Surgical site infection occurring prior to hospital discharge or up to 14 days post operation. NNIS definitions as superficial; deep or organ space N/A Patient
Notes	Overall incidence of failure to thrive in study population was 32% Funding issues/conflict of interest issues not declared	

Study ID: Porras-Hernandez 2003		
Aim of study	To determine the incidence of surgical site infection, and to identify potential risk factors associated with it	
Methods	**Design** **Duration** **No of centres** **Country (City)**	Prospective cohort study 1st August 1998 to 31st January 1999 Single site Mexico (Mexico City)
Participants	**Participants** **Age** **Gender** **Ethnicity** **Inclusion criteria** **Exclusion criteria** **Co-morbidities**	428 children undergoing general, cardiac and neuro surgery Median 27.5mth Male 56%; Female 44% From the local suburban and rural population, mainly low income families <18yrs undergoing operations Procedures without cutaneous incision; death within 48hr of surgery; abscess drainage; <30 day follow up Not reported
Definition of exposure	**Definition** **Description/classification**	Malnutrition Gomez and Waterlow's Classifications
Outcomes relevant to this	**Definition** **Description/classification**	Surgical site infection CDC criteria

review	**Study incidence of outcome** **Unit of analysis**	 18.7% Patient
Notes	Overall incidence of malnutrition in the study population was 41.6% Malnutrition not included in multivariate analysis. Funding issues/conflict of interest issues not declared	

Study ID: Rojratsirikul 2004		
Aim of study	To evaluate the preoperative nutritional status of paediatric surgical patients and to determine the validity of Subjective Global Assessment (SGA) as a screening tool for these patients	
Methods	**Design** **Duration** **No of centres** **Country (City)**	Prospective cohort study February 2001 to September 2001 Single Thailand (Songhla)
Participants	**Participants** **Age** **Gender** **Ethnicity** **Inclusion criteria** **Exclusion criteria** **Co-morbidities**	78 children aged 2mth to 16yrs admitted consecutively for mainly GI or inguino-scrotal surgery Median 4.5yr Not reported Not reported Ward admission for surgery Admissions where no surgical procedure was undertaken Not reported
Definition of exposure	**Definition** **Description/classification**	Subjective Global Assessment Class B or C Class A = well-nourished; Class B = moderate (or suspected) malnutrition; Class C = severe malnutrition (Detsky et al, 1994)
Outcomes relevant to this review	**Definition** **Description/classification** **Study incidence of outcome** **Unit of analysis**	Infectious complications (all); postoperative length of stay CDC criteria 10.3% Patient
Notes	Overall incidence of SGA malnutrition in study population was 36% Funding issues/conflict of interest issues not declared	

Study ID: Secker 2007		
Aim of study	To determine if Subjective Global Nutritional Assessment (SGNA) can predict nutrition-associated complications and length of hospital stay after surgery in children	
Methods	**Design** **Duration** **No of centres** **Country (City)**	Prospective cohort study February 2003 to August 2004 Single site Canada (Toronto)
Participants	**Participants** **Age** **Gender** **Ethnicity** **Inclusion criteria** **Exclusion criteria** **Co-morbidities**	Children undergoing non-emergency abdominal or non-cardiac thoracic surgery Mean 8.1yr, SD 6.1 yrs Male 99; Female 76 Not reported 31 days to 17.9 yrs; requiring major abdominal or non-cardiac thoracic surgery as non-emergency; no surgery performed in preceding 30 days before screening Pre-term infants not reaching 31 days corrected age; clinical instability; non-English speaking parents/carers Not reported
Definition of exposure	**Definition** **Description/classification**	Subjective global nutritional assessment Length/height; weight/height; weight percentile; BMI; mid arm circumference; triceps skinfold thickness; mid arm muscle area; handgrip strength; serum albumin, transferrin, Hb, total lymphocyte count
Outcomes relevant to this review	**Definition** **Description/classification** **Study incidence of outcome**	Infectious complications; postoperative length of stay CDC criteria for infectious complications 36%

	Unit of analysis	Patient
Notes	Overall incidence of SGNA malnutrition in study population was 51% Funding issues – supported by Canadian Doctoral Research Award Conflict of interest was not declared	

Study ID: Stey 2014		
Aim of study	To determine if children in extreme ranges of weight percentile have higher rates of postoperative complications compared with children not in the extremes	
Methods	**Design** **Duration** **No of centres** **Country (City)**	Retrospective cohort study 2011 to 2012 Multiple sites submitting data to NSQIP Pediatric Hospitals dataset USA
Participants	**Participants** **Age** **Gender** **Ethnicity** **Inclusion criteria** **Exclusion criteria** **Co-morbidities**	90,392 children undergoing all surgical procedures grouped into low weight percentile, normal weight percentile and high weight percentile Low weight mean = 6yr; Normal weight mean = 7yr; High weight mean = 10yr % Female = Low 41.7; Normal 43.04; High 44.82 Not reported Children 29 days to 18 years Neonates (defined as <28 days) as weight typically related to gestational age rather than growth Reported and stated across the three percentile groups, including immune compromise, pre-operative sepsis/infection
Definition of exposure	**Definition** **Description/classification**	Weight percentile ≤5 percentile of national age and sex-adjusted weight (Low weight percentile) Weight for age z scores from the mean of normative census data
Outcomes relevant to this review	**Definition** **Description/classification** **Study incidence of outcome** **Unit of analysis**	Surgical site infection; urinary tract infection; pneumonia National Surgical Quality Improvement Program Pediatric classification system 2% Patient
Notes	Overall incidence of children of extreme low weight percentiles in study population was 14.5% Funding/conflict of interest issues were not stated	

Study ID: Vivanco Munoz 2010		
Aim of study	To determine the incidence and risk factors for nosocomial infection in children having open-heart surgery	
Methods	**Design** **Duration** **No of centres** **Country (City)**	Retrospective cohort study January 2003 to August 2008 Single Mexico (Mexico City)
Participants	**Participants** **Age** **Gender** **Ethnicity** **Inclusion criteria** **Exclusion criteria** **Co-morbidities**	289 children requiring cardiopulmonary bypass surgery Median 10.6 mth (3 days to 36 mth) 51.9% male; 48.1% female Not stated All children < 3 yrs age during time period; undergoing first corrective surgery Non-elective surgery, previous major surgery; congenital syndromes; non-CPB surgery; oesophageal atresia; hospitalisation due to non-CHD causes; incomplete data Not reported
Definition of exposure	**Definition** **Description/classification**	Malnutrition <90% of weight/age at birth; BMI z score <-2 for BMI
Outcomes relevant to this review	**Definition** **Description/classification**	Infectious complications (all); Pneumonia (ventilation >48hrs) during PICU stay Pneumonia = clinical manifestation with positive bronchial

	Study incidence of outcome **Unit of analysis**	sample or positive CXR; mediastinitis/sepsis = when reported in medical notes 27.3% Patient
Notes	Overall incidence of malnutrition in study population was 52.6% Funding/conflict of interest issues none declared	

5b: Characteristics of excluded studies

(Listed alphabetically)

Study	Reason for exclusion
Aleissa 2011	Study investigating incidence and risk factors for deep wound infection following pediatric scoliosis surgery. No definition or assessment of under-nutrition was included.
Allpress 2004	Study looked at risk factors for SSI after pediatric cardiovascular surgery. Although patient population was <18 years, and preoperative weight was found to be associated with incidence of SSI, there was no classification of patients' nutritional status pre-operatively.
Baccari 1989	Study did not fulfil inclusion criteria. Adult patients only.
Cooper 1981	Study undertaken in a hospitalised paediatric population looking at incidence of protein calorie malnutrition. Although study included surgical participants, post-operative infectious complications were not reported.
Davenport 1993	Study undertaken in a surgical neonatal population reporting incidence of wound infection. Although birth weight was included as a pre-operative risk variable, it was not thought to be reflective of overall nutritional status.
de Souza Menezes 2012	Study population were paediatric intensive care admissions. Although nutritional assessment was undertaken for all, not all participants were surgical therefore breakdown of postoperative infectious complications were not reported.
Davis 1984	Study investigated incidence of postoperative wound infection in a children's hospital, but did not assess pre-operative nutritional status.
Doig 1976	Study looking at incidence of wound infection in a children's hospital. No pre-operative assessment of nutritional status was undertaken.
Duque-Estrada 2003	Paediatric study to determine incidence of wound infection following peditric surgery. No pre-operative assessment of nutritional status.
Glotzbecker 2013	Study was a systematic review therefore did not meet inclusion criteria.
Greco 2011	Study included both adult and paediatric participants with no breakdown of infectious complications by age, and no pre-operative nutritional assessment.
Harder 2013	Study did not fulfil inclusion criteria, as there was no nutritional assessment undertaken as part of the study methodology.
Hingorani 2011	Study into whether malnutrition at diagnosis of osteosarcoma increased risk of post-operative wound complications, but included both adult and paediatric participants with no breakdown of infection by age.
Ho 2007	Study looked at infectious complications occurring after 6 months of surgery, with no preoperative assessment of nutritional status undertaken.
Horwitz 1998	Study did not fulfil inclusion criteria, as there was no pre-operative assessment of nutritional status undertaken.
Jain 2007	Hydrocephalus patients undergoing shunt surgery. Nutritional assessment undertaken but study included both adult and paediatric participants with no breakdown of infection by age.
Jevsevar 1993	Study to determine prevalence of preoperative malnutrition and relationship to perioperative complications. Study included some adult participants with no breakdown of infection by age available for subgroup analysis.
Karpelowsky 2011	Study appeared to fulfil inclusion criteria; however, it was difficult to ascertain if malnutrition was the primary exposure leading to outcomes. In addition, outcome data was not provided according to nutritional status.
Klidjian 1980	Adolescent and adult population with mean age 56.6 years old. No breakdown of infectious complications by age category. Outcome of 'serious post-operative complication' not defined.
Labbe 1999	Case-control study to determine incidence and risk factors for surgical site infection following paediatric spinal fusion. Although weight for age was considered as a risk factor for infection, infectious outcomes were not reported according to weight for age percentile, and authors acknowledged weight for height is a more sensitive marker of nutritional status in children, but this was rarely recorded in their study population.
Leite 2005	Study did not fulfil inclusion criteria, as nutritional status was not assessed prior to surgery.
Linam 2009	Study investigated risk factors for surgical site infection following posterior spinal fusion. Although BMI was calculated, no classification of nutritional status was defined pre-operatively. Mean age 14 ½ years, with range extending to 27 years for control patients.
Study	**Reason for exclusion**

Lipton 1998	Paediatric participants with cerebral palsy undergoing spinal surgery. The majority had physical and mental disabilities, so difficult to ascertain if postoperative infectious complication (pneumonia) was related to surrogate assessments of nutrition or restricted postoperative mobility.
Mangukia 2013	Study was a review article of mediastinitis following pediatric cardiac surgery, not reporting primary data.
Markel 2008	Study appeared to fulfil inclusion criteria; however there was no recognised classification of poor nutrition, there was a higher incidence of high BMI which may be associated with steroid use, and outcome data was not presented by BMI category.
Mehta 2000	Retrospective cohort study to determine risk factors for sternal wound and other infection following paediatric cardiac surgery. No preoperative classification of nutritional status was undertaken.
Ratanachu-Ek 2011	Study to determine incidence of wound infection following paediatric surgery. No nutritional assessment undertaken prior to surgery.
Rodriguez 2013	Foreign language article potentially meeting inclusion criteria. Prospective cohort study of children with acyanotic congenital heart disease and increased pulmonary blood flow undergoing cardiac surgery. Pre-operative assessment of nutritional status - Group 1 = malnourished n=13, Group 2 = normally nourished n=15. Incidence of postoperative infection primary outcome measure.
Rosanova 2009	Study methodology did not include the assessment of preoperative nutritional status.
Rose 2012	Case series report, and although study appeared to meet inclusion criteria, it was impossible to determine if outcomes were related to immunosuppression rather than nutritional status.
Sepehr 2009	Study included both adult and paediatric participants with no breakdown of infectious complications by age.
Sharma 1986	Study to identify the extent of postoperative wound infection and identify associated risk factors. Assessment of nutritional status was not undertaken as part of the methodology.
Symreng 1983	Although study included paediatric participants aged 16 years, the majority were adults (mean age 55 years), with no breakdown of complication data by age category.
Tan 1992	Although study included paediatric participants, the majority were adults and there was no breakdown of complication data by age category.
Togo 2011	Study was a short report on risk factors for SSI. Method for classification of malnutrition was not defined, nor was timing of this assessment.
Uludag 2000	Study to determine incidence of surgical site infection in children. No weight data or other assessment of nutritional status was reported.
Wakita 2011	Study did not include infectious complications as an outcome measure.
Weber 1995	Although study appeared to meet inclusion criteria, there was no separation of infectious complications from non-infectious complications after surgery. Complication rate by nutritional status was not reported.
Willis 2009	Before and after analysis of outcome following the implementation of nutritional guidelines following Fontan completion. Methodology did not meet review inclusion criteria, and nutritional status was not defined in either cohort.
Yamamoto 1999	Study included paediatric participants, however the majority were adults (median age 37 yr) with a range of 15 – 70 years. There was no breakdown of infectious complications by age provided.

5c: References of excluded studies

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Appendix 6: Personal communications (Systematic review)

Re: query regarding 1995 article
Sat 13/09/2014 13:42
To:
Dear Ms. Hill,

Thank you for your interest in our study. Answering to your question, no one well-nourished patient had post-operative infection. Infection occurred only in the malnourished patients.
Some flaws in the translation to English can be detected in this publication. Actually, 8 patients from the high risk group (and not 9 as it was shown in table 3) developed infection. Infection incision and mediastinitis occurred both in the same patient.

Nutritional status was classified according to modified Waterlow criteria. I have the raw data from this study in case you want to use another criteria for nutritional status classification.

We have also reported association between nutritional parameters and postsurgical oucomes in two further publications:
Pediatr Crit Care Med 2001;2:29-35 and *Nutrition 2005*;21:553–558.

Please, let me know if you need any further information.
Best regards,

Heitor Pons Leite

On Fri, Sep 12, 2014 at 12:54 PM, Rebecca Hill <RHill1@uclan.ac.uk> wrote:
Dear Dr Leite

I hope you do not mind me contacting you. I am a children's cardiac nurse undertaking a PhD at the University of Central Lancashire in Preston, England.

I have read with interest your research looking at nutritional assessment and surgical risk following pediatric heart surgery, published in 1995.
I am currently undertaking a systematic review looking at surgical infectious outcome in malnourished children, and I would very much like to include your study.

Unfortunately, I am unable to calculate from the published data if any of the reported infectious complications occurred in children who were not malnourished. I am aware that the overall incidence of malnutrition was 90% in the high risk group, but I would like to clarify if possible if either pneumonia, mediastinitis, sepsis or incision infection occurred in any of the eutrophic children?

I am hoping you may still be able to help answer this, despite publication being 19 years ago, and I would be delighted to hear from you.

Kind regards,

Rebecca Hill

Re: A query regarding your 1993 article "The relationship between preoperative nutritional status and complications after an operation for scoliosis in patients who have cerebral palsy"

Fri 26/09/2014 02:12
To:
Rebecca,

It has been awhile, but I recall only looking at children under the age of 18. I hope that helps.

Dave
David S. Jevsevar, MD, MBA
djevsevar@gmail.com

On Sep 23, 2014, at 2:45 PM, Rebecca Hill wrote:

Dear Dr Jevsevar

I hope you do not mind me contacting you. I am a children's cardiac nurse currently enrolled on an MPhil/PhD programme at the University of Central Lancashire in Preston, England.

I have read with interest your research article looking at preoperative nutritional assessment in cerebral palsy patients undergoing scoliosis repair and incidence of postoperative complications. I am currently undertaking a systematic review looking at surgical infectious outcome in malnourished children, and I would very much like to include your study.

However, the population I am investigating are children less than 18 years of age, and although I can calculate the number of children meeting my inclusion criteria from the data for Group 1, I am unable to determine the number of children less than 18 years for Group 2. I am aware that it has been a long time since you undertook this research, but I am hoping you may still be able to answer this query. I would be delighted to hear from you.

Kind regards,

Rebecca Hill

Appendix 7: Quality assessment (Systematic review)

7a: Risk of bias table for cohort studies

Moderate quality of evidence

Study ID: Stey 2014		
Domain	**Judgment**	**Support for Judgment**
Representativeness of exposed cohort	Unclear Excluded <28 days of age, those with missing weight data, extreme weight outliers (>5 SD); Participants recruited from voluntary database records	"accrued into the dataset at participating NSQIP Pediatric hospitals" "neonates…were not included in this study, as their physiology is not generally believed to be comparable with that of older children"
Selection of the non-exposed cohort	Adequate From the same dataset	
Ascertainment of exposure	Adequate Less than 6th percentile of age and sex adjusted weight	
Demonstration that outcome was not present at start of study	Adequate Postoperative complications and SSI	
Comparability of cohorts	Adequate	"multivariate logistic regression was then performed…when controlling for procedure case mix and other important clinical factors"
Assessment of outcome	Adequate Outcome definitions defined, and extracted from dataset records	"postoperative complications are rigorously defined and are generally treated as dichotomous variables with unique data fields" "postoperative complications are logged for up to 30 days postoperatively"
Duration of follow-up sufficient	Unclear No reporting of any operations using implants, not their duration of follow up (usually one year)	"..whether any superficial, deep or organ space surgical site infection occurred within 30 days postoperatively"
Adequacy of follow-up	Adequate All participants accounted for in analysis	
Other potential risk of bias		

Study ID: Anderson 2011		
Domain	**Judgment**	**Support for Judgment**
Representativeness of exposed cohort	Unclear Case series of all children undergoing a specific type of cardiac surgery, therefore unlikely to be transferable to other surgical populations; Excluded participants with premature birth, chromosome abnormality or other major congenital system abnormality	

Selection of the non-exposed cohort	Adequate Same operation during the same time period without infection	
Ascertainment of exposure	Adequate Weight for age and height for age Z scores calculated from retrospective data	"we identified patients who met criteria for failure to thrive at the time of their Fontan who had WAZ below -2.0"
Demonstration that outcome was not present at start of study	Adequate	
Comparability of cohorts	Adequate Homogeneous group due to inclusion criteria; Analysis adjusted for	"..predictor variables for multivariate modelling had a p value of less than 0.1 on bivariate analysis"; "Multivariable analyses were performed using linear regression"
Assessment of outcome	Unclear Only definition provided was for pneumonia, otherwise outcome definition/classification not reported. Likely to be as per CDC criteria.	"documented significant postoperative infections including bacteraemia, mediastinitis, culture-positive urinary tract infections, culture-positive gastroenteritis, and pneumonia"
Duration of follow-up sufficient	Unclear Not stated	
Adequacy of follow-up	Adequate All participants accounted for in the analysis	
Other potential risk of bias		

Low quality of evidence

Study ID: Secker 2007		
Domain	**Judgment**	**Support for Judgment**
Representativeness of exposed cohort	Unclear Consecutive patients meeting inclusion criteria enrolled. Excluded <31 day corrected gestational age; emergency surgeries; non-English speakers; clinically unstable patients; patients undergoing surgery 30 d before screening	
Selection of the non-exposed cohort	Adequate Same population as exposed cohort	
Ascertainment of exposure	Adequate Patients screened and grouped according to nutritional status prior to surgery	"reproducible and valid technique"
Demonstration that outcome was not present at start of study	Adequate	"Children were deemed eligible if they…had not undergone surgery in the 30 d prior to screening"
Comparability of cohorts	Unclear Table with overall cohort characteristics reported, but not broken down by exposure groups. Co-morbidity burden high, but not reported by group	"although heterogeneous in terms of age, distribution by age group was fairly even"
Assessment of outcome	Adequate Medical record linkage	"the development of nutrition-associated infectious and non-

		infectious morbidities…according to published criteria"
Duration of follow-up sufficient	Adequate	"children were followed an a purely observational fashion, from the day of surgery until 30 d after surgery"
Adequacy of follow-up	Adequate Abdominal and noncardaic thoracic surgery – deemed unlikely to use implants.	"patients were followed for 30 d after surgery for the development of NACs related to their surgical procedure"
Other potential risk of bias		

Study ID: Rojratsirikul 2004		
Domain	**Judgment**	**Support for Judgment**
Representativeness of exposed cohort	Unclear Excluded participants less than 2 months old	"included consecutive pediatric patients aged 2 months to 16 years"
Selection of the non-exposed cohort	Adequate Same population as exposed cohort	
Ascertainment of exposure	Adequate Independent verification by two study authors	"data from the SGA history was summarized into…A-well nourished, B-moderately malnourished…C-severely malnourished"
Demonstration that outcome was not present at start of study	Adequate	"data regarding disease, operation and operative morbidity were also collected"
Comparability of cohorts	Inadequate No confounders adjusted for either in methodology or analysis	
Assessment of outcome	Adequate	"verification of … infection used definitions …according to the CDC"
Duration of follow-up sufficient	Adequate	"Operative morbidity defined as a complication that occurred within the 60th postoperative day"
Adequacy of follow-up	Adequate All participants accounted for in the analysis	
Other potential risk of bias		

Study ID: Hatlen 2010		
Domain	**Judgment**	**Support for Judgment**
Representativeness of exposed cohort	Unclear Appears a small number of participants for a 44 year time period; Reported inconsistent participant characteristic data	"59 patients with MMC who underwent spinal fusion and instruemtation procedures from 1974 to 2007"; "Of total, 31 were female and 29 were male"; "About 41 patients had only one spinal operation…"
Selection of the non-exposed cohort	Adequate Selected from the same population during the study period	"the study period covered 44 years… there were no differences in rate of infection over 10-year eras"
Ascertainment of exposure	Unclear	"patients were classified into two

	Used surrogate markers of nutrition to classify nutritional status	groups based on their preoperative nutritional status"; "poor nutritional status was defined as a serum albumin level less than 55 g/L or a Hct equal to or less than 33"
Demonstration that outcome was not present at start of study	Adequate Record linkage	"Data were collected from the Patient Data Management System...and hospital records"
Comparability of cohorts	Unclear Study stratified patients into nutritional and/or positive urine cultures. No adjustment for confounders in the analysis	"Fisher Exact probability test and chi square analysis….tests compared the postoperative complication rate with the surgeon; preoperative nutritional indexes; number of operations; presence or absence of UTI; the degree of curvature..."
Assessment of outcome	Adequate Although use of a recognised classification system not reported, definitions consistent	"wound infection was defined as wound breakdown with purulence, exposed spinal instrumentation, or a positive wound culture"
Duration of follow-up sufficient	Adequate Records were reviewed beyond 1 year, consistent with use of implants	"95% of complications arose within less than 1 year of the index surgery with 100% emerging before 3 years"
Adequacy of follow-up	Adequate All patients reported, with individual patient data provided for both exposure groups	
Other potential risk of bias		

Study ID: Porras-Hernandez 2003		
Domain	**Judgment**	**Support for Judgment**
Representativeness of exposed cohort	Unclear Excluded 19% of potentially eligible cohort i.e. patients dying <48hr of operation; or with incomplete follow up after discharge. Characteristics of excluded patients reported.	"530 patients underwent operation in the general surgical, cardiovascular, and neurosurgical wards. A total of 428 (80.7%) children completed follow up."
Selection of the non-exposed cohort	Adequate Same population as exposed cohort	
Ascertainment of exposure	Unclear Cut-off values for malnutrition were not explicitly reported. Likelihood is that malnutrition was defined as predicted weight for age <90%	"Nutritional condition was somatometrically evaluated by use of Gomez and Waterlow classifications"
Demonstration that outcome was not present at start of study	Adequate Record linkage	"followed-up daily until hospital discharge…complete chart review was done on postoperative day 30 for each patient"
Comparability of cohorts	Unclear Did not account for severity or risk of surgery	"Age and degree of operative contamination were adjusted for multivariate analysis"
Assessment of outcome	Adequate Likely to be study authors collecting data, but lack of blinding unlikely to cause bias.	"Superficial incisional, deep incisional, and organ/space SSI were determined according to current CDC definitions"

Duration of follow-up sufficient	Unclear Implants were used in some surgeries (e.g. ventriculo-peritoneal shunts) where CDC requires follow up to 1 year	"followed-up at the hospital clinics, and a complete chart review was done on postoperative day 30 for each patient…. If an implant wasxleft in place, complete chart reviews were done on postoperative day 30 and 6 months after the procedure"
Adequacy of follow-up	Adequate Missing data regarding antibiotic prophylaxis and open drainage systems, with numbers, sufficiently reported.	"All patients were followed up daily during the postoperative period until hospital discharge…then they were followed up at the hospital clinics"
Other potential risk of bias		

Study ID: Leite 1995		
Domain	**Judgment**	**Support for Judgment**
Representativeness of exposed cohort	Unclear Small number in cohort for a 2 yr prospective study. Inclusion and exclusion criteria not explicitly stated	"50 cardiopathic children chosen for selective cardiosurgery…were evaluated"
Selection of the non-exposed cohort	Adequate Same population as exposed cohort	
Ascertainment of exposure	Adequate Waterlow Criteria	"the percentage of weight per height located below percentile 10"
Demonstration that outcome was not present at start of study	Adequate Unit of analysis was patients with infection	"followed regarding… postoperative evolution until leaving hospital"
Comparability of cohorts	Inadequate No confounders adjusted for either in methodology or analysis	
Assessment of outcome	Adequate Classification system referenced	"Postoperative morbidity was described as the presence of complications requiring specific therapy…proposed by Buzby et al"
Duration of follow-up sufficient	Unclear No statement regarding length of follow up provided	
Adequacy of follow-up	Adequate All participants accounted for	
Other potential risk of bias		

Study ID: Vivanco-Munoz 2010		
Domain	**Judgment**	**Support for Judgment**
Representativeness of exposed cohort	Inadequate 490 charts evaluated over study period, 201 excluded (>20%)	
Selection of the non-exposed cohort	Adequate From same population during study period	
Ascertainment of exposure	Unclear Use of BMI < 2 years of age not	"malnutrition was defined as <90% of weight/age at birth and a z-score

	validated	of < -2 for BMI index before surgery
Demonstration that outcome was not present at start of study	Adequate Unit of anlysis patients not procedures	
Comparability of cohorts	Adequate Stratification according to risk score; multivariate analysis undertaken adjusting for variables	"stratified according to RACHS score"; "adjusted analyses were done 1) including pre, and transurgical variables, and 2) pre, trans and postsurgical variables"
Assessment of outcome	Adequate Clinical notes Unclear if outcome assessors blinded to exposure, but unlikely to be affected	"type of infection was obtained from the clinical notes…considered positive only when reported in the notes"
Duration of follow-up sufficient	Inadequate Length of stay on ICU before diagnosis of infection reported as median 3 days, range 2 – 9 days, no statement regarding follow up for non-infected patients; no statement regarding use or follow up of implants	"infection was determined during the patient's stay in the PICU"
Adequacy of follow-up	Adequate All patients accounted for in the analyses	
Other potential risk of bias		

Very low quality of evidence

Study ID: Al Bassam 1994		
Domain	**Judgment**	**Support for Judgment**
Representativeness of exposed cohort	Unclear Appears a small sample size for an 18 month study period	"only major and intermediate surgical procedures were selected for this study"
Selection of the non-exposed cohort	Adequate Drawn from the same surgical population during the study period	
Ascertainment of exposure	Adequate Used recognised classification systems	"recorded on day of admission – weight, height, triceps skin fold, serum albumin and haemoglobin"
Demonstration that outcome was not present at start of study	Adequate Chest infection contra-indication for surgery	
Comparability of cohorts	Inadequate No data provided across groups, no confounders accounted for/adjusted for within the design or analysis.	
Assessment of outcome	Unclear Variable reporting of patients and procedures in data tables, with procedures reported as "No. of patients". No statement provided regarding multiple infection in the same patient	"some patients were admitted more than one time because of stated surgery and in every case, pre-operative nutritional assessment and post-operative course were monitored"; "six patients had post-operative complications…five patients had

		chest infection"
Duration of follow-up sufficient	Inadequate Mean hospital stay reported as 14 days, with range 2 to 46 days. Less than 30 days	"postoperative morbidity was monitored during hospitalization"
Adequacy of follow-up	Unclear Variable reporting of patients and procedures, no outcome table regarding infection provided, no statement provided regarding missing data	
Other potential risk of bias	Clustering	

Study ID: Bhattacharyya 1990, 1993		
Domain	**Judgment**	**Support for Judgment**
Representativeness of exposed cohort	Unclear Study excluded incomplete data and death within one month of surgery	"32 had incomplete data… and 6 patients died within a month of surgery"
Selection of the non-exposed cohort	Adequate Drawn from the same surgical population within the study period	
Ascertainment of exposure	Adequate Recognised classification system	"441 of 615 patients studied had normal nutrition"
Demonstration that outcome was not present at start of study	Unclear Some patients required more than one operation; time interval between operations not specified	"608 patients who underwent a total of 676 operations"
Comparability of cohorts	Inadequate No confounders accounted for in methodology, not adjusted for in analyses	
Assessment of outcome	Adequate Variable reporting of cohort numbers noted for outcomes within and across papers; Unclear if outcome assessors blinded to exposure group and its effect on outcome reporting However - Recognised outcome classification systems used, and both papers reported outcomes by nutritional status which consistent in terms of numbers.	"Fourteen of the 17 patients who developed wound infection were personally examined by one or both of the authors"; "one of the two authors personally examined 33 of the 38 patients who developed nosocomial infection"
Duration of follow-up sufficient	Unclear Likely that follow up occurred up to 30 days, but not explicitly stated. Median time interval between operation and occurrence of wound infection reported as 5 days (range 4 to 37) and nosocomial infection reported as 7 days (range 2 to 45)	"Inpatients were examined daily … until discharge or for 4 weeks after operation. Patients undergoing ligation of patent ductus arteriosus were transferred postoperatively to the pediatric service; their wounds were followed for 2 weeks after operation"; "surveillance of inpatients…was conducted daily during hospital rounds… surveillance of inpatients and outpatients…was conducted by weekly chart review"

		"Patients were seen on average 1 week after discharge and periodically thereafter until they were well"
Adequacy of follow-up	Unclear Not clearly stated Variable reporting of patients and procedures within and across papers	
Other potential risk of bias	Clustering due to multiple operations, non-consistency of patient/procedure numbers between papers despite identical datasets	"676 consecutive patients"; "608 patients who underwent a total of 676 operations"; "441 of 615 patients had normal nutrition"

7b: Risk of bias table for case control studies

Low quality of evidence

Study ID: Farley 2014		
Domain	**Judgment**	**Support for Judgment**
Case definition adequate	Unclear Methods section does not include deep SSI definition, although CDC definition is referred to in introduction, so likely to be consistent with CDC. Delayed SSI defined as >1yr post-surgery Power calculation for large differences (80% power to detect odds ratios of 2.1)	"patients who developed a deep SSI"; "hospital committee tracks SSI's after spinal deformity surgery"; "we collected all of our patients with infections from a 5 year period"
Representativeness of cases	Adequate	"infected patients were consecutive…all patients followed for at least 2 years postoperatively"
Selection of controls	Adequate Total number of operations from which controls were selected not reported	"control patients were consecutive from the same time period"
Definition of controls	Adequate Controls selected from same surgical population	"scoliosis surgery without the development of SSI"
Comparability of cohorts	Unclear Ambulatory status provided within table; continence, although recorded, was not reported No adjustments made in the analysis	"not a matched study"; "similar diagnoses, age, and sex" "methods used…did not control for potentially confounding variables"
Ascertainment of exposure	Inadequate BMI cannot be calculated in children < 2 years old, when used for 2 – 19 year olds it must be adjusted for age and sex	"BMI was calculated from height and weight"
Same method of ascertainment of exposure for both cases and controls	Adequate Individual patient BMI data provided for both cases and controls (Table 1)	
Non-response rate	Adequate Results presented for all 20 cases and 50 control patients	
Other potential risk of bias		

Study ID: Nateghian 2004		
Domain	**Judgment**	**Support for Judgment**
Case definition adequate	Adequate No power calculation provided; Allow SSI definition stated, duration of follow up was insufficient	"National Nosocomial Surveillance System definitions were used to classify SSI"; "practitioners followed patients to detect the occurrence of SSI from the time of surgery until hospital

		discharge or for 14 days, whichever occurred first"
Representativeness of cases	Unclear	"Controls were selected from the cohort of…patients who had not developed an SSI"
Selection of controls	Adequate	"using a random number generator, one control was then selected for each case"
Definition of controls	Adequate	"eligible controls were matched with cases according to age, NNIS risk score and year of surgery"
Comparability	Unclear Methodology matched on age, duration of surgery, wound class, and physical status score (ASA), but no group data provided. No multivariate analysis was undertaken as part of the analysis	
Ascertainment of exposure	Adequate Determined from medical records	"presence of failure to thrive defined as weight >2 SD below the norm for age"
Same method of ascertainment of exposure for both cases and controls	Adequate Same method for both groups, results reported	"Failure to thrive = Cases: 39%, Controls 24%"
Non-response rate	Adequate Missing data reported, unlikely to affect outcome	"Data are missing for 4 cases and 2 controls"
Other potential risk of bias		

Appendix 8: Additional tables (Systematic review)

8a: Reporting of mortality across all included studies

Study	Participants	Study mortality	Comments
Al Bassam (1994)	74	None	
Anderson (2011)	55	None	
Bhattacharyya (1990,1993)	615	1.1%	5 deaths within 1 week of surgery excluded from study
Farley (2014)	57	Not reported	
Hatlen (2010)	69	Not reported	
Leite (1995)	50	4%	2 deaths in high surgical risk group
Nateghian (2004)	76	Not reported	
Porras-Hernandez (2003)	403	9.6%	"not related to SSI"
Rojratsirikul (2004)	78	Not reported	
Secker (2007)	175	Not reported	
Stey (2014)	80,743	0.15%	
Vivanco_Munoz (2010)	276	15%	In patients with infection

8b: Prognostic Indicators of undernutrition across all included studies

Study	Prognostic indicator for undernutrition	Classification for presence of undernutrition	Validity of Indicator	Comments
Al Bassam (1994)	Weight for height; Height for age; Triceps skin fold; Serum albumin; Haemoglobin;	Weight for height <90% of standard; Height for age <95% of standard; Triceps skin fold <35%; Serum albumin: <3g/dL (0-5yr) or <3.5g/dL (6-12yr); Hb: <10g/dL (1-3yr) or <10.5g/dL (3-6yr) or <11 g/dL (6-12yr)	Anthropometry valid; biochemical markers and cutoffs for undernutrition in children not validated	
Anderson (2011)	Weight for age Z score	WAZ less than –2 SDS	Valid	
Bhattacharyya (1990,1993)	Waterlow's Criteria	Weight for height <80% of norm	Valid	
Farley (2014)	Body mass index	BMI below 18.5	BMI classification used in adults.	BMI percentile should be used for 2 to 19yr olds.
Hatlen (2010)	Serum albumin, Haematocrit	Albumin < Hct <	None	Surrogate markers, reliability in categorising nutritional status undetermined.
Leite (1995)	Waterlow's Criteria; Triceps skin fold; Brachial muscle circumference;	Weight for height <10th percentile; Triceps skin fold <5% percentile; BMC <5%	Valid	
Nateghian (2004)	Weight	Weight for age less than -2 SDS	Valid	
Porras-Hernandez (2003)	Waterlow's Criteria, Gomez	Weight for height or weight for age <90% of norm	Valid	
Rojratsirikul (2004)	Subjective global assessment		Valid	
Secker (2007)	Subjetive global assessment		Valid	
Stey (2014)	Weight percentile	Weight percentile < 5th percentile	Not validated, but comparable to SDS	Cut-off lower than other measures, so may underestimate undernutrition by comparison
Vivanco-Munoz (2010)	Weight for age @ birth. BMI Z scores	Weight for age at birth <90% BMI Z score < 2 SDS	No validity for infants without centile reference; BMI Z scores valid only in children over 2	Unclear interpretation of nutritional risk classification

8c: Summary of Findings

Outcome: Surgical site infection

Study ID	Study unit of analysis	Exposure		No exposure		No. analysed	Relative risk / Odds ratio	95% Confidence interval	Analysis	Reported/ Calculated
Bhattacharyya 1990	Operations n= 615	Malnutrition		Normal nutrition		615	RR 1.06	0.38 - 2.95	Unadjusted	Calculated
		Events	Totals	Events	Totals					
		5	174	12	441					
Farley 2014	Patients n= 70	BMI <18.5		BMI 25.0 – 29.9		54 1 case and 4 controls >18 yrs excluded; 12 participants overweight/obese excluded	OR 2.1	0.61 – 7.30	Unadjusted	Calculated
		Events	Totals	Events	Totals					
		10	29	5	25					
Hatlen 2010	Operations n= 84	Poor nutritional status		Normal nutritional status		69 15 participants with positive urine cultures excluded	RR 3.35	1.51 – 7.45	Unadjusted Unadjusted	Reported Calculated
		Events	Totals	Events	Totals					
		11	22	8	39					
Nateghian 2004	Patients n=76	Failure to thrive		Normal		76	OR 2.1	0.65 – 6.84	Unadjusted	Calculated
		Events	Totals	Events	Totals					
		15	24	23	52					
Porras-Hernandez 2003	Patients n=428	Malnutrition		No malnutrition		403 25 overweight participants excluded	OR 0.7 RR 0.68	0.4 – 1.02 0.45 – 1.03	Unadjusted Unadjusted	Reported Calculated
		Events	Totals	Events	Totals					
		28	178	52	225					
Stey 2014	Patients n=90,392	Low weight percentile		Normal weight percentile		80,743 9,649 participants >95th weight percentile excluded	RR 1.33 OR 0.89	1.17 – 1.5 0.77 – 1.02	Unadjusted Adjusted	Calculated Reported
		Events	Totals	Events	Totals					
		321	13,095	1,246	67,648					

Outcome: Any postoperative infection

Study ID	Study unit of analysis	Exposure		No exposure		No. analysed	Relative risk / Odds ratio	95% CI	Analysis	Reported / Calculated
Anderson 2011	Patients n=55	Failure to thrive		Normal growth		55	0.33	0.22 - 0.44	Multivariate	Reported
		Events	Totals	Events	Totals		3.6	1.17 – 11.05	Unadjusted	Calculated
		4	10	5	45					
Leite 1995	Patients n= 50	Malnutrition		No malnutrition		50	Risk difference 20.5%		Unadjusted	Calculated
		Events	Totals	Events	Totals					
		8	39	0	11					
Rojratsisrikul 2004	Patients n = 78	SGA malnutrition		No SGA malnutrition		78	Risk difference 28.6%		Unadjusted	Calculated
		Events	Totals	Events	Totals					
		8	28	0	50					
Secker 2007	Patients n=175	SGNA malnutrition		SGNA no malnutrition		175	RR 1.53	1.02 – 2.32	Unadjusted	Calculated
		Events	Totals	Events	Totals					
		39	90	24	85					
Vivanco-Munoz 2010	Patients n=289	Malnourished		Normal		276 13 overweight participants excluded	RR 0.86	0.46 – 1.44	Unadjusted	Calculated
		Events	Totals	Events	Totals					
		38	152	36	124					

Outcome: Septicaemia

Study ID	Study unit of analysis	Exposure		No exposure		No. analysed	Relative risk	95% CI	Analysis	Reported / Calculated
Bhattacharyya 1993	Operations n= 615	Malnutrition		No malnutrition		615	RR 6.34	2.01 – 19.94	Unadjusted	Calculated
		Events	Totals	Events	Totals					
		10	174	4	441					

Outcome: Pneumonia

Study ID	Study unit of analysis	Exposure		No exposure		No. analysed	Relative risk / Odds ratio	95% CI	Analysis	Reported / Calculated
Al Bassam 1994	Operations n= 74	Protein calorie malnutrition		No malnutrition		74	No events in normal weight cohort		Unadjusted	Calculated
		Events	Totals	Events	Totals					
		5	59	0	15					
Bhattacharyya 1993	Operations n=615	Malnutrition		Normal nutrition		615	RR 10.14	2.17 – 47.27	Unadjusted	Calculated
		Events	Totals	Events	Totals					
		8	174	2	441					
Stey 2014	Patients n=90,392	Low weight percentile		Normal weight percentile		80,743 9,649 participants >95th weight percentile excluded	2.69	2.13 – 3.41	Unadjusted	Calculated
		Events	Totals	Events	Totals					
		106	13,095	203	67,648					
Vivanco-Munoz 2010	Prolonged mechanical ventilation group n= 267	Malnourished		Normal		256 11 overweight participants excluded	RR 0.68	0.32 – 1.18	Unadjusted	Reported
		Events	Totals	Events	Totals					
		24	138	30	118					

Outcome: Urinary Tract Infection

Study ID	Study unit of analysis	Exposure		No exposure		No. analysed	Relative risk	95% CI	Analysis	Reported / Calculated
Stey 2014	Patients 90,392	Low weight percentile		Normal weight percentile		80,743	RR 1.84	1.51 – 2.23	Unadjusted	Calculated
		Events	Totals	Events	Totals					
		136	13095	382	67648					
Bhattacharyya 1993	Operations n=615	Malnutrition		Normal nutrition		615	RR 10.14	1.14 – 90.07	Unadjusted	Calculated
		Events	Totals	Events	Totals					
		4	174	1	441					

Outcome: Length of stay

Study	Length of stay reported	Location of central tendency and estimate of spread in exposed group	Location of central tendency and estimate of spread in non-exposed group	Significance	Calculated mean/median difference	Calculated confidence intervals	Comments
Anderson 2011	Postoperative	Median 11.5 days (range 7 – 51)	Median 8 days (range 5 – 31)	p =0.06**	3.5*		On multivariate testing p = 0.6
Rojratsirikul 2004	Postoperative	12 days	4.5 days	p = <0.01*	7.5*		No reported estimate of spread by group
Secker 2007	Postoperative	Mean 8.2 days (SD ±10 days)	Mean 5.3 days (SD ±5.4 days)	p = 0.001**	2.9**	0.52 – 5.3	Study reported 2.9 d (55%) longer postoperative stay for malnourished children although CI consistent with no effect

*calculated, **reported,

Appendix 9: CDC (2012) Criteria for diagnosis of surgical site infection (SSI)

Superficial SSI (SSSI) must meet one of the following criteria:

- Involves only skin and subcutaneous tissue of the incision
- Patient has at least **one** of the following:
    - Purulent drainage from the superficial incision
    - Organisms isolated from an aseptically-obtained culture of fluid or tissue from the superficial incision
    - pain or tenderness; localized swelling; erythema; or heat **and** superficial incision is deliberately opened by surgeon and are culture positive or not cultured
    - diagnosis of SSI by surgeon or attending physician

Deep incisional SSI

- Occus within 30 days of an operation if no implant left in place
- Involves deep soft tissues of the incision (for example, fascial and muscle layers)
- Patinet has at least **one** of the following:
    - Purulent drainage from the deep incision
    - Spontaneous dehiscence, or is deliberately opened or aspirated by a surgeon and is culture positive or not cultured
    - Fever (>38°C); localized pain or tenderness
    - Diagnosis of SSI by surgeon or attending physician

Organ/space SSI

- Occus within 30 days of an operation if no implant left in place
- Involves any part of the body (excluding skin, fascia, or muscle layers) opened or manipulated during the operative procedure
- Patient has at least **one** of the following:
    - Purulent drainage from a drain that is placed into the organ/space
    - Organisms are isolated from aseptically obtained culture of fluid/tissue
    - Evidence of abscess formation within the organ/space
    - Diagnosis of organ/space SSI by surgeon or attending physician (e.g. endocarditis, mediastinitis)

Appendix 10: Ethics approval form for Study 2 (University of Central Lancashire)

uclan
University of Central Lancashire

3rd October 2013

Bernie Carter and Rebecca Hill
School of Health
University of Central Lancashire

Dear Bernie & Rebecca

Re: BuSH Ethics Committee Application
Unique Reference Number: BuSH 201

The BuSH ethics committee has granted approval of your proposal application 'Nutrition and surgical site infection in a paediatric cardiac surgical population'.

Please note that approval is granted up to the end of project date or for 5 years, whichever is the longer. This is on the assumption that the project does not significantly change, in which case, you should check whether further ethical clearance is required

We shall e-mail you a copy of the end-of-project report form to complete within a month of the anticipated date of project completion you specified on your application form. This should be completed, within 3 months, to complete the ethics governance procedures or, alternatively, an amended end-of-project date forwarded to roffice@uclan.ac.uk quoting your unique reference number.

Additionally, BuSH has listed the following recommendation(s) which it would prefer to be addressed. Please note, however, that the above decision will not be affected should you decide not to address any of these recommendation(s).

Should you decide to make any of these recommended amendments, please forward the amended documentation to roffice@uclan.ac.uk for its records and indicate, by completing the attached grid, which recommendations you have adopted. Please do not resubmit any documentation which you have **not** amended.

Yours sincerely

Denise Forshaw
Chair
BuSH Ethics Committee

Appendix 11: SSI Care bundle for paediatric cardiac surgery

Preoperative phase

1. **Screen and decolonise Staphylococcus aureus carriers prior to surgery**
   Screen emergency patients on admission if likely to need cardiac surgery

   Provide parent information letter (pre-surgery)

   If positive result start prescribed decolonisation ASAP and treat for 5 days irrespective of surgery date

2. Perform **preoperative antimicrobial skin cleansing the night before and day of surgery** if negative or SA result unknown
   Use Octenisan (wipes or bath solution). If known skin allergy/eczema/sensitive skin, please use Oilatum Plus.

Intraoperative phase

3. Administer **cardiac surgical antibiotic prophylaxis** as per Trust guidelines (including additional cover for chest explorations/closures on PICU)
4. Allow alcoholic **skin preparation to air-dry** prior to draping
5. **Minimise door openings** and theatre traffic during all operations (including chest explorations/closures on PICU)
6. **Hats and masks to be worn** correctly by all staff present in theatre during periods of tray preparation and whilst the chest is open.

Postoperative phase

7. Administer **cardiac surgical antibiotic prophylaxis** as per Trust guidelines (see attached)
8. **No toys/personal items** to be placed on ICU bed/cot
9. Strict **hand-hygiene** prior to contact of patient/patients environment
10. Protect sternotomy/thoracotomy wounds with a **sterile dressing for 48hr postoperatively**
    a. If post-op ECHO/ECG requires removal of sternotomy dressing during first 48hr, this will be done using sterile equipment and re-dressed according to the Surgical Wound Care ANTT guidance.
    b. Document subsequent dressing changes after 48hr
    c. If child remains intubated after 48hr, reapply clean dressing to wound to protect from respiratory secretions.
11. **Surgical Wound Care ANTT** for all postoperative dressing changes, including drain removal.

Appendix 12: Additional tables (Cohort study)

12a: Maximal model

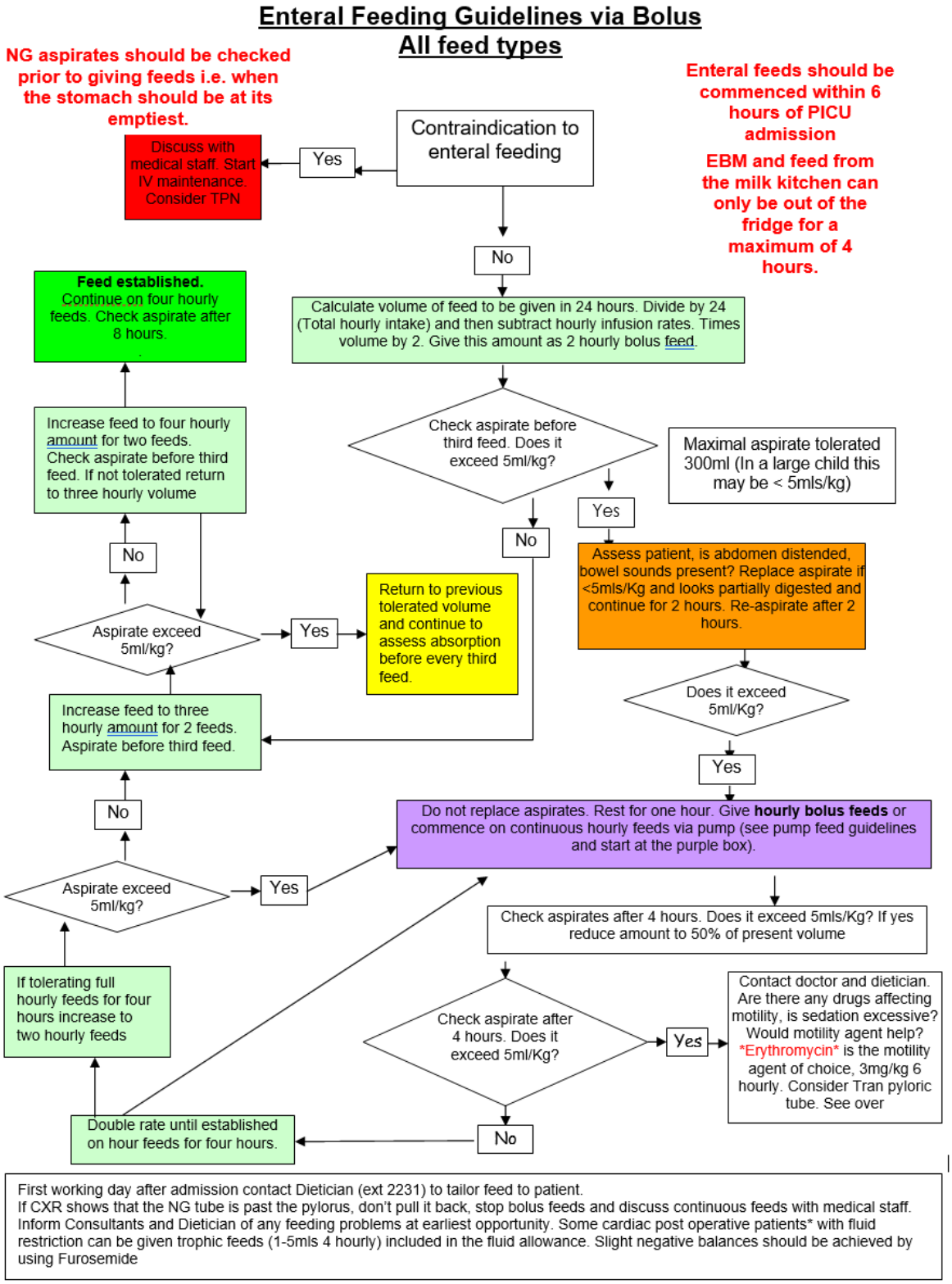
Variables in the equation (N=652)		n	Multivariate analysis Odds ratio	*p* value
Age category	Neonate	144	1	
	Infant	254	0.33 (0.15 – 0.71)	0.005
	Preschool	126	0.32 (0.12 - 0.86)	0.025
	School age	128	0.21 (0.07 - 0.60)	0.004
Weight for age Z-score (WAZ) category	WAZ < -2	184	0.56 (0.29 - 1.10)	0.092
	WAZ -2 to +2	458	1	
	WAZ > +2	10	1.25 (0.13 - 11.91)	0.846
Preoperative serum haemoglobin	Low	68	0.97 (0.45 - 2.07)	0.929
	Normal	502	1	
	High	82	2.30 (1.02 -5.17)	0.044
Theatre team	1	235	1	
	2	213	1.20 (0.68 - 2.13)	0.534
	3	204	0.58 (0.29 - 1.14)	0.111
Operation complexity score	0 to 3	67	1	
	3.1 to 6	166	0.65 (0.20 - 2.09)	0.469
	6.1 to 9	327	0.92 (0.31 - 2.74)	0.884
	9.1 to 12	70	0.60 (0.15 - 2.39)	0.467
	12.1 to 15	22	0.73 (0.14 - 3.70)	0.703
Delayed sternal Closure	No	568	1	
	Yes	84	1.17 (0.52 - 2.66)	0.705
Use of ECMO	No	642	1	
	Yes	10	2.32 (0.51 - 10.52)	0.275
Preoperative length of stay in days	0	174	1	
	1	257	0.69 (0.34 - 1.40)	0.302
	2 to 3	63	1.06 (0.40 - 2.82)	0.902
	4 to 7	73	1.08 (0.42 - 2.78)	0.880
	8 or more	85	1.55 (0.63 - 3.82)	0.338

12b: Minimal model

Variables in the equation (N=654)		n	Multivariate analysis Odds ratio	*p* value
Age	Neonate	144	1	
	Infant	254	0.28 (0.14 -0.53)	<0.001
	Preschool	126	0.25 (0.11 -0.55)	0.001
	School age	130	0.17 (0.07 - 0.40)	<0.001
Weight for age *z*-score (WAZ) category	WAZ < -2	184	0.58 (0.30 - 1.12)	0.101
	WAZ -2 to +2	460	1	
	WAZ > +2	10	1.15 (0.13- 10.60)	0.901
Preoperative serum haemoglobin	Low	69	1.04 (0.50 - 2.15)	0.917
	Normal	503	1	
	High	82	2.30 (1.09 - 4.85)	0.029
Theatre team	1	235	1	
	2	215	1.21 (0.69 - 2.12)	0.497
	3	204	0.57 (0.30 - 1.10)	0.095

Appendix 13: Study site feeding guidelines

13a: Enteral feed progression guideline (PICU)



13b: Fasting guidance (PICU)

Guidance on fasting times on PICU

Procedure	Prior to	Afterwards
Extubation	4 hours	4 hours
Intubation	4 hours	Start feeds immediately when stable after intubation
Respiratory physiotherapy	Do NOT routinely stop continuous feeds for this. The physios should be able to time their treatments around the child's feeds (in most cases). Once the child has assessed, if they need treatment, they will ask you to stop the feed and aspirate the NGT completely. Immediately after the treatment is finished then replace this feed and restart the feeds.	
Bronchoscopy in an intubated child	DO not stop feeds JUST aspirate NGT completely before procedure	Restart feeds as soon as bronchoscopy finished
For CT/MRI	Do NOT stop feeds, just completely aspirate the NGT before leaving	Restart as soon as back in PICU – check position of NGT
Tracheostomy change (1st time)	4 hours + aspirate NGT before procedure	Once changed and OK restart feeds immediately
Other tracheostomy changes (routine)	Do not stop feeds, just stop & aspirate before procedure	Once done, replace aspirate and recommence feeds
Chest drain removal on an intubated child	Do NOT stop feeds	
Chest drain removal on an extubated child – depends on sedation required for removal But if Sevo or ketamine	4 hours before and aspirate NGT prior if having Servo or ketamine sedation	Start feeds again once awake
Re-taping of an ETT	Do not stop feeds – just aspirate NGT prior to taping	Once re-taped, replace aspirate and recommence feeds
GA (eg for chest closure)	Do not stop feeds just aspirate NGT completely before procedure	Re-start feeds once finished
Proning (prone positioning)	Do not stop feeds but completely aspirate NGT before proning	Re-start feeds once stable prone and NGT position reconfirmed

Appendix 14: Ethics approval form for Study 3 (University of Central Lancashire)

9 December 2016

Margaret Hurley / Rebecca Hill
School of Nursing
University of Central Lancashire

Dear Margaret / Rebecca

Re: STEMH Ethics Committee Application
Unique Reference Number: STEMH 591

The STEMH ethics committee has granted approval of your proposal application 'Feeding practices and related outcomes in neonates undergoing surgery for congenital heart disease'. Approval is granted up to the end of project date* or for 5 years from the date of this letter, whichever is the longer.

It is your responsibility to ensure that

- the project is carried out in line with the information provided in the forms you have submitted
- you regularly re-consider the ethical issues that may be raised in generating and analysing your data
- any proposed amendments/changes to the project are raised with, and approved, by Committee
- you notify roffice@uclan.ac.uk if the end date changes or the project does not start
- serious adverse events that occur from the project are reported to Committee
- a closure report is submitted to complete the ethics governance procedures (Existing paperwork can be used for this purposes e.g. funder's end of grant report; abstract for student award or NRES final report. If none of these are available use e-Ethics Closure Report Proforma).

Yours sincerely

Emma Hesketh
University Officer for Ethics
STEMH Ethics Committee

Appendix 15: Data extraction form (Case study)

Study ID:

Date of birth: Age at surgery:

Date of hospital admission:

Date of PICU admission:

Date of surgery:

Diagnosis:

Operation:

Diagnostic category:

<u>Preoperative data collection:</u>

Patient: Antenatal CHD diagnosis: yes / no

Gender: M / F

Gestation: __ /40

Post-gestational age at time of operation:

Known genetic abnormality:

APGAR: @1min @5min @10min

Birth weight:

Birth length:

Prostaglandin infusion: Y / N Dose: _____ nanogram/kg/min

Pre-op oxygen saturations: ___ %

Supplemental O2: Y / N FiO2/Flow:

Pre-op mechanical ventilation: Y / N Pre-op Optiflow: N / Y Flow (l/min):

Feeding method: IVT / Oral / NGT/ OG / PN

Type of milk: Breast / Standard IF / HE formula

Max feeding volume preoperatively (highest 24hr intake): _____ ml/kg/day

Venous access sites: Peripheral Umbilical Longline CVL
Location: _____ _____

Biochemistry:
- Urea
- Creatinine
- CRP
- Albumin
- Protein
- Hb
- WCC
- Lymphocytes

Onodera's Prognostic Nutritional Index:

Surveillance swab results: Rectal
Nasal
Groin

Other:

Intraoperative data collection:

Weight at op:

Length at op:

PRAiS score:

ASA score:

Antibiotic prophylaxis: @induction / @incision Repeat dose @3hr: Y / N

Central venous line placement: L / R IJV / Femoral / Other _____

Steroid administration: Y / N Dose:

Duration of surgery (mins):

CPB: N / Y (min): _____ Aortic cross clamp: N / Y (min):_____

Lowest operative body temperature:

Highest glucose:

Highest lactate:

Red cell transfusion (units): Adult packs _____ Paediatric packs _____

Platelets: N / Y Dose (ml): _____

Cryoprecipitate: N / Y Dose (ml): _____

Albumin transfusion: N / Y Dose (ml/kg) _____

Delayed sternal closure: Y / N If open, skin closure: Y / N

ECMO @ end of surgery: Y / N

Drains placed: Mediastinal / Left pleural / Right pleural

PD catheter: N / Y

Pacing wires: N / Y Atrial / Ventricular

PICU admission data:

Admission ICU severity score (PIM2):

Core body temp on arrival:

Vasoactive inotrope score (VIS) on arrival:

Adrenaline

Noradrenaline

Dopamine

Dobutamine

VIS:

Rhythm on arrival:

Temporary pacing: N/ Y

FiO_2:

Mean airway pressure:

PaO_2:

Oxygenation Index:

Chest: Closed / Open with membrane / Open with skin closed

ECMO : No / Yes via chest / Yes via neck

Flow:

Sweep:

FiO_2:

PICU data extraction form Study ID:_____

PICU DAY	1	2	3	4	5	6	7	8	9	10	11	12	13	14 …….
Weight														
HR (H)														
HR (L)														
Paced?														
MBP (H)														
MBP (L)														
Body temp (H)														
Body temp (L)														
Active cooling? If y, target T														
Paralysis														
Intubation														
Mean airway pressure (cmH_20)														
FiO_2 (H)														
SaO_2 (H)														
SaO_2 (L)														
pH (L)														
PaO_2 (L)														
PCO_2 (H)														
Glucose (H)														
Glucose (L)														
Lactate (H)														
OI (H)														
ECMO														
Adrenaline														
Noradrenaline														
Dopamine														
Dobutamine														
Milrinone														
Vasopressin														

Other:														
VIS highest														
Hb (L)														
WCC (H)														
Neutrophils (H)														
Lymphocytes (H)														
Urea (H)														
Creatinine (H)														
Albumin (L)														
Total protein (L)														
CRP (H)														
Blood Tx (units/ml)														
Albumin Tx (ml/day)														
Gelofusine (ml/day)														
Clotting factor Tx (ml/day)														
IV drug/infusions (ml/day)														
IV maintenance (ml/day)														
Enteral feeding (Y/N)														
Time to first feed (hr)														
Parenteral nutrition (ml/day)														
Enteral nutrition target (ml/day)														
Actual enteral nutrition (ml/day)														
Enteral nutrition route (NGT/OGT/JT)														
Formula type/EBM														
Continuous (ml/hr: duration)														
Bolus feed (ml/feed: frequency)														
Gastric residual volume (ml/day)														
Feeding interuption (NBM) in last 24hr?														
NBM reason?														
NBM total hrs/24hrs														
Calorie intake/24hrs														

Peritoneal dialysis (Y/N)														
Urine output (ml/day)														
Chest drain output (ml/day)														
Peritoneal output (ml/day)														
Gastric/other output (ml/day)														
Total output (ml/day)														
Overall fluid balance														
Fluid overload calculation														
CVL day														
Arterial line day														
IV sedation														
IV opiate														
Enteral sedation														
Enteral opiate														
Diuretic therapy (IV/O) (mg/day)														
Steroid administration														
If yes, cortisol level														
Antibiotic therapy														
Diagnosed infection														
If yes, source														
Critical event*														
Procedure*														
Other														

Summary @PICU discharge:

CVL days: _____

Chest drain days: _____

Maximum enteral feeding volume (ml/kg/day): _____

Post PICU data extraction form Study ID:_____

DATE														
Weight														
HR (H)														
HR (L)														
MBP (H)														
RR (H)														
RR (L)														
MBP (L)														
SaO_2 (H)														
SaO_2 (L)														
Body temp (H)														
Body temp (L)														
Hb (L)														
WCC (H)														
Neutrophils (H)														
Lymphocytes (H)														
Urea (H)														
Creatinine (H)														
Albumin (L)														
Total protein (L)														
CRP (H)														
Blood Tx (units)														
Albumin Tx (ml/day)														
Parenteral nutrition (ml/day)														
Enteral nutrition target (ml/kg/day)														
Enteral nutrition (ml/day)														
Enteral nutrition route (O/NGT/OGT/PEGT/JT)														

Breast / Formula type														
Continuous (ml/hr: duration)														
Bolus feed (ml/he: frequency)														
NBM in last 24hr?														
NBM reason?														
NBM total hrs/24hrs														
Feeding complication*														
Fluid therapy (IV or diorylyte)														
Total fluid intake (IV + E)														
Calorie intake/day														
Urine output (ml/day)														
Chest drain output (ml/day)														
PD output (ml/day)														
Gastric/other output (ml/day)														
Total fluid output (ml/day)														
Overall fluid balance (ml/day)														
Fluid overload calculation														
CVL day														
Milrinone														
IV sedation														
IV opiate														
Enteral sedation														
Enteral opiate														
Furosemide (mg/day)														
Spironolactone (mg/day)														
Steroid administration														
If yes, Cortisol level														
Antibiotic therapy														
Diagnosed infection														
If yes, source														
Critical event*														
Procedure*														
Other														

Hospital discharge data collection:

Feeding achievement:	Breast on demand	Y / N
	< 6mth >150ml/kg/day	Y / N Volume: ____
	>6mth >120ml/kg/day	Y/ N Volume: ____

Feeding mode: Breast / Bottle / Tube _____

Discharge weight:

Discharge WAZ:

Discharge weight – birth weight (g):

Discharge weight – operative weight (g):

Growth velocity (weight at discharge - lowest recorded weight to weight / day

***Adverse event checklist:**

CA = Cardiac arrest
EE = Emergency ECMO
CE = Emergency chest re-exploration/re-opening
NEC = Necrotising enterocolitis (or gut ischaemia)
AKI = Acute renal failure
FE = Failed extubation/reintubation
OP = Cardiac re-operation within 14 days of initial surgery/PICU
C = NICOR complication
D = Death
IR = ICU readmission

***Clinical procedure checklist:**

DSC= Delayed sternal closure
E = Planned extubation
DR = Drain removal
DI = Drain reinsertion
I = Investigation requiring interdepartmental transfer
Op= Elective non-cardiac re-operation

Feeding complication checklist:

GRV = high gastric residual volumes
US = Unsafe swallow
BA = Bilious aspirates
DE = distended abdomen
FI = feeding intolerance (D±V)

Appendix 16: Neonatal chronologies (Case study)

16a: Neonates with minimally interrupted feeding

Neonate 3 was born at term with an antenatal diagnosis of Transposition of the great arteries (TGA) with intact ventricular septum (IVS). Birth weight was within a normal WAZ category. She was born in good condition, intubated and ventilated and stabilised on prostaglandin infusion prior to immediate transfer to the PICU where she was scheduled for a balloon atrial septostomy. Following this procedure, she was extubated and was transferred to the cardiac ward. Prostaglandin was weaned and discontinued on day 6 of life, she was commenced on a gentle dose of diuretic, and remained clinically stable with oxygen saturations of 91%, feeding mainly via nasogastric tube but with 5 to 10 ml orally per feed, to a maximum preoperative volume of 140ml/kg/day. Onodera's PNI was 51, and preoperative Staphylococcus aureus status was negative.

On day 15 of life, she had her cardiac surgery. At this point her weight remained within a normal WAZ category, and she had regained her birth weight. The risk of operation was predicted at 1.5%, and on ICU admission postoperatively her paediatric index of mortality (PIM2) score was 2.3%. Inotrope score was 7.5, with an oxygenation index of 4, with blood loss from chest drains peaking at 20ml/kg/day on the day of surgery, prior to removal on postoperative day 2 (24 hours after chest closure). Maximum non-nutritive fluid intake was on operative day, at 53ml/kg/day.

Enteral feeding commenced 8 hours post ICU admission, and maximum nutritive intake achieved during the stay was 47ml/kg/day. Feeds were disrupted on postoperative day 1 for delayed sternal closure, and again for extubation the following day. Once feeds had been commenced, disruption of feeds amounted to a total of 22 hours. She was transferred to the cardiac ward on postoperative day 3, on a weaning dose of milrinone which was discontinued the following day.

Feeding attainment rapidly increased following transfer to the ward, with enteral feeds via nasogastric tube reaching 120ml/kg/day by postoperative day 5 and 150ml/kg/day by postoperative day 6. Oral feeds were introduced, with standard formula swapped to high energy to promote weight gain. A wound healing disturbance was noted on postoperative day 5, with dehiscence and a tissue fluid leak but no evidence of surgical site infection.

Swallowing was somewhat uncordinated, therefore a video-fluroscopy was performed on postoperative day 11 as the majority of feeds still remained via nasogastric tube. The investigation was normal and oral feeding gradually improved with time. At hospital discharge, baby had established full breastfeeding and was thriving. Weight at hospital discharge on postoperative day 31 remained within a normal WAZ category, with an overall postoperative growth velocity of 28.6 g/day. Her wound was healing well but still under review by the surgical team at the time of discharge.

Neonate 4 was also antenatally diagnosed with TGA_IVS and born at term within the normal range for gestational size, and within a normal WAZ category. He was born in reasonable condition, with transfer to the study hospital on day one of life having been established on a prostaglandin infusion. After arrival at the study hospital, he underwent a balloon atrial

septostomy in the cardiac catheterisation laboratory, before being extubated the following day and being discharged to the cardiac ward. Preoperative Staphylococcus aureus status was negative.

On day 10 of life, he underwent surgery. At this time, he had regained his birth weight, was feeding at 120ml/kg/day, and his preoperative nutritional risk score was 50.7. Surgical risk was 1.14%, and on admission to intensive care, PIM2 risk was 2.9% on minimal inotropic support and with a closed chest.

Enteral feeding commenced 27 hours after admission once serum lactate was less than 2 mmol/L. Maximum non-nutritive fluid intake was 126ml/kg/day on the operative day, with minimal bleeding and an overall output of 95ml/kg/day. Feeds were disrupted for extubation on postoperative day 3, and overall fluid balance was negative at the time of ICU discharge on postoperative day 4.

Maximum feeding on PICU was 75ml/kg/day on postoperative day 4 and following transfer to the ward breastfeeding supplemented bottle feeding. Thereafter further calculation of nutritional intake was not possible but maximum documented bottle feeds equalled 110ml/kg/day. Weight on postoperative day 5 demonstrated a postoperative weight gain of 160g, and baby was discharged home on postoperative day 7 fully breastfeeding, but with no further weight measurement documented.

Following discharge, on postoperative day 19 parents requested surgical review for a wound healing problem. A stitch abscess was diagnosed at the proximal sternotomy wound and he was started on antibiotics and the wound healed two weeks later.

Neonate 6 was a term baby transferred to the study hospital at 2 days of age with an antenatal diagnosis of pulmonary atresia with ventricular septal defect (VSD), stable on prostaglandin infusion. He remained on the cardiac ward for a period of 22 days before surgery, at which time he had achieved enteral feeding volumes of 120ml/kg/day via bottle and nasogastric feed supplementation. He had achieved a weight gain of 310g prior to surgery, with a nutritional risk score of 71.45. Weight at birth and at time of surgery were appropriate for gestation and age. His preoperative Staphyloccoccus aureus status was negative.

Following palliative surgery (BT-shunt) with a surgical risk of 5.3% performed at 25 days of age, on admission to intensive care his chest was open, inotrope score was 9 and PIM2 score was calculated at 1.7%. Non-nutritive fluid intake was at a maximum of 130ml/kg/day on postoperative day 1, which coincided with a maximum inotrope score of 26. Enteral feeding commenced 14 hours after ICU admission, but feeds were disrupted for 8 hours for possible chest closure on postoperative day 1, and again for 11 hours on postoperative day 2 when the chest was closed. Feeds were disrupted again on postoperative day 4 for extubation, and he was transferred to the cardiac ward the following day. Enteral feeding had been slow to advance on ICU due to multiple feeding disruptions, with a maximum volume of enteral intake of 40ml/kg/day (and below minimal recommended intake for ICU) by the time of discharge to the ward.

Once on the cardiac ward, feeding improved dramatically with 120ml/kg/day of high energy formula achieved on postoperative day 6, and he was discharged home fully orally feeding on

postoperative day 8. Weight at discharge demonstrated a 50g increase from weight at surgery. No postoperative complications were experienced.

Neonate 9 was born at term with an antenatal diagnosis of TGA_VSD. She was born in good condition within a normal weight category. Started on prostaglandin infusion after delivery she required intubation for apnoea after 5 hours. Following extubation on day 3 of life she began to desaturate 48 hours later, requiring reintubation. Due to risk factors being present for neonatal infection – PROM >24hr and maternal Group B Streptococcus – she received 48 hours of antibiotics until all cultures returned as negative. She was transferred self-ventilating to the cardiac ward on day 7 of life, and as admission screening swabs were noted to grow Staphylococcus aureus, five days of decolonisation treatment was undertaken prior to surgery. Preoperative feeds were 120ml/kg/day via nasogastric tube, and calculated PNI was low at 35.7 due to a preoperative albumin level of 14g/dl. Preoperative Staphylococcus aureus status was positive, and she received 5 days of decolonisation treatment prior to surgery.

Surgery occurred on day 18 of life, with a surgical risk of 1.4%. After an uneventful operation, with minimal bleeding, she was admitted to the intensive care unit with her chest open, and a maximum inotrope score of 28.5, with a PIM2 risk of 2.2%. Feeding commenced 17 hours post admission once lactate had settled <2mmol/L. Feeds were disrupted for attempted chest closure on postoperative day 2, but was not tolerated due to cardiovascular instability, with feeds disrupted again on postoperative day 4 when the chest closure was tolerated. At this point, overall fluid balance was negative 300, and maximum feeding volumes at 85ml/kg/day.

There was a further feed disruption on postoperative day 6 for extubation and she was transferred to the cardiac ward the following day having achieved a maximaum enteral feed intake of 84ml/kg/day whilst on intensive care. Feeds were via nasogastric tube, and 24-hours post ward transfer she was noted to have a disorganised swallow. Over the course of the next five days feeding co-ordination improved and she was discharged home on postoperative day 14 fully feeding via bottle, having remained in a normal WAZ category.

Neonate 11 was a term baby of normal weight for gestational age who presented at day 13 of life at his local hospital with apnoea and cyanosis. He was intubated and ventilated, with chest x-ray demonstrating cardiomegaly. On arrival to the intensive care unit he was on mechanical ventilation, stable on a prostaglandin infusion and low dose inotropic support, with a PIM2 at 5%. Following echocardiogram a postnatal diagnosis of hypoplastic aortic arch and VSD was confirmed. He was fed via nasogastric tube at a volume of 70ml/kg/day. Preoperative PNI was 50.95. Preoperative Staphylococcus aureus swabs were negative.

Surgery was performed at 21 days old, with a predicted operative mortality of 3.3%. At the end of surgery, the chest was left open, maximum inotrope score was 18 on postoperative day 1 and oxygenation index was 9.6. Enteral feeds commenced 5 hours after ICU arrival as lactate remained less than 2 mmol/L.

Feeds were disrupted for 5 hrs on postoperative day 2 for chest closure, and again for extubation on postoperative day 4 for a total of 7 hours. By the time of discharge on postoperative day 6 he was achieving enteral feed volumes of 90ml/kg/day via nasogastric tube. Cumulative percent fluid balance at the time of ICU discharge was negative 17.5%.

Feed volumes of 120ml/kg/day were achieved following ward transfer on postoperative day 6, with 150ml/kg/day of oral feeds achieved the following day. Weight demonstrated a decreasing trend postoperatively, with weight at discharge on postoperative day 8 recorded as 3.52kg, minus 180g from operative weight, equally a net postoperative weight loss of 3.2g/day. No postoperative complications were experienced.

Neonate 12 was an antenatal diagnosis of hypoplastic aortic arch with VSD born at 40+6 weeks gestation, requiring stimulation, suction and inflation breaths post-delivery. Spontaneous respirations were present within 2 – 3 minutes, but due to concerns over possible neonatal sepsis, a course of antibiotics commenced for a duration of 48hr. He was commenced on prostaglandin infusion at 5 nanogram/kg/minute and transferred to the cardiac ward at the study hospital on day 1 of life.

Preoperative albumin levels were not recorded, therefore nutritional index was unable to be calculated. He achieved a maximum enteral intake of 135ml/kg/day prior to surgery, with appropriate size for gestational age and within the normal range of weight for age z-score category. Preoperative Staphylococcus aureus swabs were negative.

His operation was performed when he was 9 days old, with a predicted risk of 0.8%. PIM score on ICU admission was 3.4%, with a maximal inotrope score of 15 on admission and oxygenation index of 6.2. His chest was closed at the end of the procedure, and enteral feeding commenced 19 hours post ICU admission once his initial lactate of 2.41 decreased to <2mmol/L.

Cumulative fluid balance on day 2 was 5% positive, although by the time of discharge on postoperative day 3 cumulative balance had decreased to 1% positive. Enteral feeding was disrupted for a duration of 17 hours on postoperative day 2 for drain removal and extubation. Maximum enteral intake on intensive care reached 27ml/kg/day via nasogastric tube, significantly under his projected daily intake of 70ml/kg/day.

On the day of transfer to the cardiac ward on postoperative day 3, enteral feeding had reached 120ml/kg/day via a combination of oral and nasogastric tube feeds. Body weight on transfer demonstrated a 370g increase, which had reduced to 3.74kg on diuretics by the time of hospital discharge. Postoperative weight velocity was negative, equalling a deficit of 14g/day.

No postoperative complications were experienced, and he was discharged home uneventfully, fully feeding via bottle at 135ml/kg/day on postoperative day 7 within a normal WAZ category.

Neonate 14 was born large for gestational age at 39 weeks. He was noted to have grunting and respiratory distress soon after delivery and following a trial of non-invasive respiratory support was intubated and ventilated. Congenital heart disease was suspected due to low preductal oxygen saturations. Prostaglandin infusion was commenced at 100 nanograms/kg/min, and the baby was transferred to the intensive care unit. Echocardiogram on admission confirmed transposition of the great arteries with intact ventricular septum, therefore an emergency septostomy was performed.

He was successfully extubated and transferred to the cardiac ward prior to surgery. Enteral feeds were established preoperatively at 150ml/kg/day via a combination of oral bottles and nasogastric tube feeds. Onodera's nutritional index score was calculated at 66, and weight at

time of surgery was within a normal WAZ category. Preoperative Staphylococcus aureus status was not performed.

Operative risk was estimated at 2.3%, and PIM2 on ICU admission postoperatively was 1.8%. Chest was left open at the end of the procedure, and maximum inotrope score was 9 on day of surgery. Enteral feeds were commenced 18 hours after admission, and disrupted on postoperative day 1 for chest closure, and again on postoperative day 3 and 4 for attempted extubation and successful extubation respectively. He was transferred to the cardiac ward in the afternoon of postoperative day 4 following extubation earlier that morning. Maximum feeds on intensive care reached 43 ml/kg/day via nasogastric tube. Cumulative fluid balance on day 2 was negative, and this trend increased by the time of ICU discharge.

On the day of transfer, enteral feeds were administered via nasogastric tube at 75ml/kg/day. The following day breast feeds were established on demand. Recorded weight at the time of hospital discharge demonstrated a postoperative weight loss of 430g. No postoperative complications were experienced.

Neonate 17 was a term baby born in good condition at an appropriate size for gestational age. She was noted to be dusky on the postnatal ward with low oxygen saturations, therefore was transferred to the neonatal unit and commenced on antibiotics following a septic screen. A local echocardiogram diagnosed structural heart disease, therefore baby was started on prostaglandin and transferred to the intensive care unit at the study hospital on Day 2 of life. Admission PIM2 score was 1.8%. Diagnosis was confirmed as total anomalous pulmonary venous drainage (TAPVD) and she was listed for surgery. Preoperative enteral feeding was established via nasogastric tube at a volume of 112ml/kg/day. Onodera's PNI was calculated at 50. Preoperative Staphylococcus aureus status was confirmed as negative.

Surgical risk was predicted at 2.2%, and surgery was performed on day 7 of life. Chest was closed at the end of the operation, and she returned to intensive care in stable condition with a maximum inotrope score of 10 and oxygen index of 13.8. Enteral feeds were started 15 hours after admission when lactates stabilised. Feeds were disrupted on two occasions for a total of 11 hours during ICU stay, both extubation related. Chest drains were removed on postoperative day 2, with extubation the following day. Cumulative fluid balance on day 2 was negative 2.5%, increasing to negative 11% by the time of PICU discharge on postoperative day 3. Maximum nutritional intake whilst on PICU was 41ml/kg/hr.

Weight on postoperative day 5 demonstrated a postoperative weight loss of 200g, and she was discharged home on postoperative day 6 without further weight measurement, having established of 55-60 ml orally every 3 – 4 hours (approximately 130 ml/kg/day). Last recorded weight remained within a normal WAZ category. No post-operative complications were experienced.

Neonate 18 was born at 37 weeks with intrauterine growth retardation noted on the 20/40 foetal scan. He was both small for gestational age and in an underweight WAZ category at birth, and although initially born in good condition, was noted to be dusky and apnoeic on the postnatal ward therefore was transferred to the neonatal intensive care unit where he was found to have a metabolic acidosis, therefore was intubated, ventilated and commenced on prostaglandin infusion prior to transfer to the intensive care unit at the study hospital on day 1 of life.

Echocardiogram confirmed a postnatal diagnosis of double outlet right ventricle (DORV) with pulmonary atresia and VSD, and once he had been stabilised, he was extubated and transferred to the cardiology ward for close observation and growth prior to a plan for palliative surgery. Feeds were changed to high energy formula at a volume of 135ml/kg/day to optimise calories and growth. Over the following three weeks weight increased by 450g, although Onodera's PNI was unable to be calculated as no serum albumin measurement was taken preoperatively. However, at the time of surgery he remained in an underweight WAZ category. Preoperative Staphylococcus aureus status was negative.

Surgical risk was estimated at 14.3% and a central shunt was performed at 27 days of age. PIM2 score on ICU admission was 2.8%, and he returned with an open chest. Highest inotrope score was 20 on the day of surgery, with moderate ventilation requirements. Feeds were commenced 21 hours after admission, with some delay caused by failed pH testing of nasogastric tube position necessitating CXR confirmation of tube position. Feeds were subsequently disrupted for delayed sternal closure on postoperative day 2, and for extubation on postoperative day 5, totalling 29 hours of his 140-hour stay. Maximum feeding volume at ICU discharge on postoperative day 6 had been 57ml/kg/day.

Lowest recorded weight after transfer to the cardiology ward demonstrated a weight loss of 130g. Oral diuretics were subsequently discontinued, and weight began to increase over the next few days. Weight at discharge on postoperative day 10 was recorded at 2.6kg, with an established oral feeding volume of 135ml/kg/day of high energy formula. WAZ category at time of hospital discharge remained in the underweight category. No complications following surgery occurred.

Neonate 20 was born at an appropriate size for gestational age. Although not requiring resuscitation following delivery, she was treated with antibiotics for 10 days due to an 11-hour history premature rupture of membrane and suspected sepsis prior to discharge home. She presented at her local emergency department on day 22 of life following an episode of being grey, floppy and mottled at home, and although initially managed with intravenous therapy and antibiotics, required intubation and ventilation following profound oxygen desaturation. As she was noted to have a difference in upper and lower body perfusion and thready femoral pulses, she was commenced on prostaglandin infusion prior to transfer to the intensive care unit where echocardiogram confirmed the postnatal diagnosis of TAPVD. Admission PIM2 score was 7.4%. Admission weight fell within an underweight WAZ category, and Onodera's nutritional index was calculated as 41. Although screening for MRSA was negative, no swabs were performed to determine Stapylococcus aureus status prior to surgery.

Following stabilisation in her overall condition, enteral feeds were commenced via nasogastric tube at 75ml/kg/day overnight prior to being placed NBM for surgery at 10am the following morning. Surgical risk was 4.6% and following surgery she returned to ICU with her chest closed, and an inotrope score of 8. Chest drain losses were minimal (<2ml/kg/hr) with moderate peritoneal drain losses on postoperative day 1 (2.5ml/kg/hr). Cumulative fluid balance was negative 5% on day 2, and negative 13.7% on ICU discharge. Enteral feeding commenced 8hrs after ICU admission once serum lactate was <2mmol/l, and she achieved a maximum intake 69ml/kg/day prior to discharge to the ward, somewhat hindered by feeding disruptions – one related to a transiently increased serum lactate on postoperative day 1, and two related to extubation attempts on postoperative day 2 and 3. Consequently, feeds were

withheld for 31% (27hr out of 86hr) of her ICU stay, with IV therapy utilised as an alternative source of hydration.

Drain removal occurred on postoperative day 3 prior to an uneventful extubation into nasal cannula oxygen. Transfer to the cardiac ward occurred the following day. Enteral feeds via bottle were quickly re-established to a volume of 150ml/kg/day at hospital discharge on postoperative day 8. Last recorded weight was on postoperative day 5, demonstrating an overall postoperative weight deficit of 100g (minus 12.5g/day). No postoperative complications were recorded at the time of discharge, although surgical site infection occurred two weeks after discharge on postoperative day 23, which required hospital readmission and intravenous antibiotics. Wound culture swabs at this time were positive for Staphylococcus aureus.

16b: Neonates with moderately interrupted feeding

Neonate 15 was an antenatal diagnosis of hypoplastic left heart syndrome (HLHS) born at 37 weeks gestation at an appropriate size for age. He was delivered in good condition, at normal size for gestational age, and commenced on a prostaglandin infusion at 5 nanogram/kg/min soon after delivery as per antenatal plan. Due to the presence of risk factors a septic screen was taken, and he commenced a 5-day course of antibiotics prior to transfer to the cardiac ward at the study hospital. Initially serum lactate levels were elevated, so he was initially kept nil by mouth.

Feeds were introduced following transfer, with a maximum preoperative feeding volume of 125ml/kg/day. On day 6 of life, he underwent a cardiac MRI scan to further delineate his cardiac anatomy, before going for his surgery on day 14 of life. Preoperative Staphylococcus aureus swabs were negative, and surgical risk was estimated at 14.6%.

His operation was lengthy and problematic. There was dysrhythmia on initial weaning from cardiopulmonary bypass and intraoperative bleeding. Following a failed attempt to separate from bypass the operative repair was revised. After a second failed attempt with what was felt to be a good surgical repair, he was placed on extra-corporeal membrane oxygenation (a modified form of cardiopulmonary bypass) through an open chest and taken to the cardiac catheterisation laboratory to investigate possible reasons. Findings showed a descending aorta to pulmonary vein fistula, and by this time he had been in the theatre for 14 hours, with a total bypass in excess of 12 hours, so it was decided to transfer him to the intensive care unit on full-flow ECMO with a plan to coil the aberrant vessel in the next 48hr.

Admission PIM2 score was 1.3%, and there were problems with major bleeding (170ml/kg/hr in the first 5 hours) requiring massive transfusion and chest re-exploration for further haemostasis. After this his haemodynamic status improved, with heart rate normalising and cessation of inotropes early on postoperative day 1. Serum lactates remained elevated therefore enteral feeds were withheld. Parenteral nutrition was commenced on the evening of postoperative day 1 in view of renal replacement therapy in the form of continuous haemofiltration being undertaken via the ECMO circuit, which enabled full control of fluid balance.

On postoperative day 2 he underwent coiling of the aberrant vessel in the cardiac catheterisation laboratory and post-procedural serum lactates subsequently started to lower.

Following a second chest exploration on postoperative day 3 with insertion of bilateral pleural drains, enteral feeding with standard formula commenced on postoperative day 4 at which time lactate levels were less than 2mmol/l.

Despite normal cranial ultrasound scans whilst on ECMO, abnormal movements thought to be seizures were noted overnight on postoperative day 4 which responded well to phenobarbitone. Consequently, the following morning CT imaging of the brain confirmed a brain injury – widespread ischaemic changes with subdural and intraventricular haemorrhage. Following review by Neurology he was started on antiepileptics with good control of seizures.

Parenteral nutrition was continued until postoperative day 5 when enteral feed volumes had reached 52ml/kg/day. Following dietetic review, feeds were changed to high energy formula. Enteral feed disruption occurred for ECMO weaning and decannulation on postoperative day 7 and delayed sternal closure on postoperative day 9, which limited the advancement of feed volumes during this time.

Deep mediastinal swabs taken at the time of chest closure demonstrated growth of Pseudomonas, therefore a 6-week course of antibiotics was commenced for mediastinitis. Despite renal replacement therapy, cumulative fluid balance on day 2 was positive 32%, which by postoperative day 7 had reduced to 17%. Following cessation of haemofiltration with ECMO separation, renal replacement therapy changed to peritoneal dialysis, but as this was problematic, he remained in a positive cumulative fluid balance state up until ICU discharge. He was successfully extubated on postoperative day 16 having failed a ventilation weaning trial the day before. By the time of transfer to the cardiac ward on postoperative day 18 he had reached enteral feed volumes of 120ml/kg/day.

Following transfer to the cardiac ward a sedation weaning plan was required following his long intensive care stay which delayed investigation to determine whether his swallow was safe to permit oral feeds. As he failed to demonstrate a non-nutritive suck, he was listed for insertion of a gastrostomy feeding tube on postoperative day 29. At the time active follow-up was completed, he was still awaiting this procedure.

Neonate 16 also had a long and complicated postoperative stay. An antenatal diagnosis of HLHS he was born at an appropriate weight for gestational age to a mother with gestational diabetes. He was started on prostaglandin infusion as per antenatal plan, requiring phototherapy for neonatal jaundice. Following transfer to the cardiac ward, he was enterally fed to a volume of 90ml/kg/day prior to surgery, and Onodera's prognostic nutritional index was calculated at 56. Preoperative Staphylococcus aureus status was negative.

His operation was on day 6 of life with a surgical risk of 10.4%. There were intraoperative problems with bleeding and high serum lactates, therefore his chest was left open at the end of the procedure. On admission to the intensive care unit his PIM2 score was 4% with an inotrope score of 29. Due to high inotropic requirements and a low serum cortisol, hydrocortisone was started.

Postoperative bleeding was 2 ml/kg/hr but a fall in serum haemoglobin the day after surgery following recent transfusion raised concerns, and a cranial ultrasound scan was requested. Although preoperative imaging had been normal repeat ultrasound demonstrated a Grade III intraventricular haemorrhage and evidence of left peri-ventricular ischaemia. Consequently,

coupled with mild postoperative coagulopathy, routine anticoagulation was stopped to minimise the risk of further bleeding at this critical time. At this time, he remained on neuromuscular blockade with his chest open.

As lactates remained significantly elevated into postoperative day 1 with oliguria, renal replacement therapy in the form of peritoneal dialysis was commenced along with parenteral nutrition. Trophic feeds were started on postoperative day 2. Cumulative fluid balance on ICU day 2 was neutral and both cardiovascular support and ventilation were gently weaned over the following days. Delayed sternal closure occurred on postoperative day 3, with drain removal the following day.

Nutritional enteral feeding started on postoperative day 6, with parenteral nutrition continuing until postoperative day 9 at which time enteral feeds were established at 63 ml/kg/day. Feeding was disrupted on postoperative day 7 for possible extubation but was postponed due to an increased work of breathing. Feeds were disrupted again on postoperative day 8 for extubation, but he required reintubation after 6 hours. Informal diaphragm screening at that time demonstrated poor movement of his left diaphragm. On postoperative day 11 he was extubated onto non-invasive ventilation and was discharged the following day to the cardiac ward. Maximum enteral intake had reached 93 ml/kg/day.

Following transfer to the ward he remained on non-invasive ventilation until postoperative day 19, when he was trialled off. However, on postoperative day 28 he was put back on non-invasive support for increasing oxygen requirements and increased work of breathing. Formal diaphragm screening on postoperative day 34 demonstrated a left diaphragm palsy, and at completion of follow up he was waiting to return to theatre for diaphragm plication and gastrostomy tube insertion for an unsafe swallow.

He was eventually discharged home on postoperative day 67 with a discharge weight just remaining within the normal WAZ category for age.

Neonate 19 was born at an appropriate size for gestational age within a normal WAZ category. He required resuscitation at birth and spent 48-hours in the special care baby unit prior to discharge home. He presented to his local emergency department at one week of age with a 1-day history of poor feeding and increased work of breathing. He subsequently collapsed with poor systemic perfusion and oxygen saturations at 70%. He was intubated and ventilated, commenced on a prostaglandin infusion, inotropic support and was transferred to the intensive care unit at the study hospital, where he was diagnosed with interrupted aortic arch and VSD. He remained on full mechanical ventilation, prostaglandin infusion and low dose inotropic support until surgery. PIM2 score on admission to ICU was 14.6%. Although negative for MRSA, formal screening swabs for methicillin sensitive Staphylococcus aureus were not performed. However, endotracheal secretions taken on ICU admission revealed suggestive of colonisation, although preoperative decolonisation was not undertaken.

Following initial resuscitation and stabilisation on intensive care, surgery occurred 3 days after PICU admission, on day 13 of life. At this time enteral intake was 25ml/kg/hr and his weight had dropped within an underweight WAZ category. Onodera's nutritional index was calculated at 41. Surgical risk was estimated at 6.7%.

On skin incision he went into supra-ventricular tachycardia requiring pre-operative cardioversion. Once the operation was completed, there were further episodes of dysrhythmia requiring amiodarone infusion and chest re-opening. He returned to ICU with his chest open but skin closed on significant inotropic therapy with an inotropic score of 25, and amiodarone infusion. Postoperatively significant problems with malignant arrhythmia continued, with systemic hypotension. Systemic cooling to 35 degrees Celsius was performed with ongoing amiodarone infusion. Maximum inotrope score was 32 on day of surgery, with delayed sternal closure occurring on postoperative day 1. Decreasing trends in inotropic support and ventilatory requirements were observed. Enteral feeds were commenced 32 hours after intensive care admission, and as he was feeding his intravenous amiodarone was swapped to an enteral formulation.

Chest drain removal occurred on postoperative day 5 when antibiotics were started for wound dehiscence and suspicion of superficial wound infection, in the presence of raised inflammatory markers, although culture swabs taken at this time were negative. However, in the morning of the following day there was an acute deterioration with recurrence of tachyarrhythmia and a secondary low cardiac output state which required re-initiation of both high inotropic support and intravenous anti-arrhythmics. Cooling was also re-established. Serum lactate levels rose therefore feeds were disrupted, and as there was evidence of late onset acute renal dysfunction peritoneal dialysis was commenced.

Over the following 72 hours control over the tachyarrhythmia was attained, and he began to make progress once more. By postoperative day 10 his inotropic support had been discontinued and his feed volumes were at 120ml/kg/day. He was noted to be intermittently in sinus rhythm and was extubated onto non-invasive respiratory support on postoperative day 12. He continued with a mild increased work of breathing and oxygen saturations running at 92%. He was transferred to the high dependency unit on postoperative day 14 having achieved a maximum enteral intake on ICU of 160ml/kg/day of expressed breast milk.

The following day he was readmitted to the intensive care unit with a further episode of tachy-arrhythmia requiring intravenous escalation of medical therapy, in addition to concerns regarding poor gastric absorption of oral medication and feed intolerance. Following a period of stabilisation, oral anti-arrhythmic medication was re-introduced with weaning off all intravenous therapy by postoperative day 23. Feeding intolerance was a problem during this second admission with episodes of vomiting. Feeds were trialled via continuous pump, and anti-reflux medications were introduced with some effect. Throughout his readmission he remained self-ventilating on non-invasive ventilatory support in 40% oxygen and was transferred to the cardiac ward on postoperative day 23.

One day following ward transfer, fever with increasing inflammatory markers led to a septic screen, and blood cultures from his central venous line revealed growth of Staphylococcus aureus. The line was removed, and a course of intravenous antibiotics were commenced. The following day, on postoperative day 25, focal seizures were observed requiring intravenous lorazepam. A neurology referral was made in view of these new-onset seizures. Subsequent brain MRI revealed left parietal lobe changes which will require further neurology follow-up, despite no further witnessed seizures.

Temporary pacing wires were eventually removed on postoperative day 28, with 48-hr Holter monitoring showing periods of breakthrough SVT. However, he remained cardiovascularly stable through these episodes therefore was discharged home on postoperative day 42 with weekly follow-up. At this point his wound dehiscence was healing nicely and he was kept under weekly surgical review. In terms of enteral feeding, he was fully orally fed at 150ml/kg/day. However, in view of his suboptimal weight gain and the fact that he remained in an underweight WAZ category six weeks after surgery, two of his eight daily feeds were changed to high energy formula to promote catch-up growth.

16c: Neonates with severely interrupted feeding

Neonate 1 was born with an antenatal diagnosis of hypoplastic aortic arch with VSD in good condition at an appropriate size for gestational age and underwent surgery on day 10 of life within a normal weight-for-age category. Pre-operative feeding was to a maximum of 150ml/kg/day of standard formula, with no significant loss of weight loss prior to surgery. A prostaglandin infusion was running at 5 nanogram/kg/min to maintain ductal patency, with pre-operative oxygen saturations at 95%. As no serum albumin was measured pre-operatively, Onodera's PNI was unable to be calculated. Microbiological screening swabs on admission were negative for bacterial growth including Staphylococcus aureus.

Following surgical repair at an estimated risk of 4.6%, enteral feeds were withheld for 70 hours due to serum lactate levels greater than 2. Having commenced feeding, there was one feeding disruption on postoperative day 5 for extubation, for a total of 9 hours. At time of ICU discharge, the maximum enteral feeding volume attained was 69ml/kg/day.

During the second day on the ward following transfer, on postoperative day 7, there were clinical concerns raised regarding possible necrotising enterocolitis, with a raised C-reactive protein level and bilious aspirates. Following review by the general surgical team, conservative management for NEC consisting of nil by mouth, parenteral nutrition at 120ml/kg/day and antibiotic therapy for a period of five days. During this time, the lowest recorded body weight was 370g less than his operative weight, but as this was a greater than a 200g/day difference from the recorded daily weight before or after, it was consequently disregarded as a spurious result. The next lowest weight, in keeping with normal physiological trends, was 135g lower than operative weight, and therefore this was used as the nadir of weight loss on postoperative day 10. Once feeds were re-introduced on postoperative day 12, volumes quickly increased to a maximum intake of 150ml/kg/day on postoperative day 18.

On day 13 positive blood cultures were obtained from the central venous line in situ, initially placed in theatre. Antibiotics were restarted for a central line associated blood stream infection. Initially intravenous, these antibiotics were swapped to an oral dose and he was discharged home to complete a full two-week course. Last recorded body weight (two days prior to hospital discharge) was 3.29kg. Cumulative fluid overload on day 2 and day 7 PICU were 11.7% and -9.8% respectively. Maximum growth velocity during the postoperative recovery was 2.5g/day, and weight at hospital discharge demonstrated a deficit of 110g from operative weight.

In summary, he spent a total of 21 days in hospital after surgery, with a total hospital length of stay at 26 days. Two infection-related complications occurred – NEC, and line infection – of which the latter was a health-care associated infection. He was discharged home in good

health, having made a good overall postoperative recovery. Weight loss was experienced during the hospital stay, and at the time of hospital discharge he had fallen into the low weight-for-age (undernutrition) category. He was fully enterally feeding via bottle at 150ml/kg/day at the point of hospital discharge.

Neonate 8 was noted to have breathlessness and low oxygen saturations soon after birth. He was born within a normal WAZ category, in good condition. Clinical features of Trisomy 21 were noted, and chromosomal analysis confirmed this. He was initially treated as a presumed sepsis with 5 days intravenous antibiotics, prior to an echocardiogram confirming a diagnosis of structural heart disease. He was transferred to the cardiac ward on prostaglandin infusion, enterally feeding via bottle at a volume of 120ml/kg/day, with a PNI of 50.6, where his postnatal diagnosis was confirmed as interrupted aortic arch with VSD. Preoperative screening did not reveal carriage of Staphylococcus aureus.

He underwent surgical correction with an estimated risk of 4% two days later, with primary chest closure at the end of the procedure. He was admitted to the intensive care unit with a PIM2 score of 1.2%. Maximum inotrope score was 19 on the day of admission, with oxygen index initially high at 13.6. Maximum non-nutritive fluid intake was 83 ml/kg/day on operative day, with enteral feeds starting 15hr post ICU admission. Ventilation was weaned and extubation occurred uneventfully on postoperative day 2, onto non-invasive respiratory support. Feeds were increased to a maximum of 82ml/kg/day prior to discharge to the high dependency unit on postoperative day 4.

He was readmitted to intensive care on postoperative day 9 following an acute deterioration with desaturation episodes and bradycardia. Concerns were raised regarding possible central line sepsis therefore antibiotics were recommenced. In the absence of a lumbar puncture, he was also treated for possible meningitis. He was successfully extubated again on postoperative day 12 and transferred to the cardiac ward on postoperative day 14 on 93 ml/kg/day. Following these two ICU admissions, a postoperative weight loss of 380g was observed on postoperative day 15.

Following transfer, further recovery was uncomplicated. At the time of discharge on postoperative day 30, weight had increased to 3.1kg, with him fully bottle feeding at 135ml/kg/day. This was only 100g more than at the time of operation, giving an overall postoperative growth velocity of 3g/day. At time of discharge, his weight had dropped into an underweight WAZ category.

Neonate 10 was born large for gestational age, requiring stimulation and inflation breaths following delivery at term. He had an antenatal diagnosis of interrupted aortic arch with VSD and was transferred to the study hospital on day 7 of life on a prostaglandin infusion. He was fed 150ml/kg/day via bottle and nasogastric tube, with a PNI score of 60.95. Preoperative Staphylococcus aureus status was negative.

On day 11 of life, he underwent surgery with a predicted risk of 7.4%. Chest was left open at the end of the operation, and on arrival to ICU, his PIM2 score was 2.7%. Maximum inotrope score on postoperative day 1 was 37.5, with an oxygen index of 12. There was minimal bleeding, and although kidney function remained within normal parameters, peritoneal dialysis was commenced for control of fluid balance and a persistent metabolic acidosis.

Feeding commenced 33 hours following ICU admission once lactates had fallen below 2mmol/L.

His chest was closed uneventfully on postoperative day 3, with peritoneal dialysis being discontinued the following day. On postoperative day 6 he was placed nil by mouth for possible extubation, but after 11 hours with climbing carbon dioxide levels, feeds were restarted. After a further two disruptions of feeding for possible extubation, he was extubated on postoperative day 10, but required reintubation for increased work of breathing and raised carbon dioxide levels, with chest x-ray findings consistent with a lower respiratory tract infection for which he commenced antibiotics. Two days later, extubation occurred again, but once more he required re-intubation. Due to two previous failed extubations, on postoperative day 13 he went to theatre for airway investigations and was extubated at the end of this procedure as there was no evidence of airway pathology. However, again reintubation was required within 3 hours. Ventilation weaning was attempted again on postoperative day 18, but again he did not cope on minimum ventilator settings, therefore support was increased.

On postoperative day 26 diaphragm screening was performed, which revealed a left phrenic nerve palsy as the likely reason for failure to wean ventilation. Consequently, following representation at the cardiac surgical meeting he was accepted for diaphragm plication. However, on postoperative day 28 concerns regarding possible sepsis were raised and the operation was postponed. Following 5-days of intravenous antibiotics for suspected lower respiratory tract infection, he was taken to theatre on postoperative day 32 and the operation was performed.

An MRI scan was performed on postoperative day 39, with ventilation slowly weaning but complicated by sedation withdrawal syndrome. Unfortunately, he was diagnosed with ventilator-associated pneumonia on postoperative day 44, again requiring antibiotic therapy and preventing any further progress with ventilation weaning.

Following a long and complicated postoperative recovery, and after 47 days on ICU, he was successfully extubated and discharged to the cardiac ward the following day. Despite multiple feeding disruptions for extubation attempts and airway related investigations, in the absence of ongoing heart failure, he demonstrated postoperative weight gain on enteral nutrition at 145ml/kg/day via nasogastric tube. At the time of ICU discharge, weight had increased by 520g, averaging a daily weight gain of 11g/day whilst on ICU.

Following transfer to the ward, he required a weaning regime for sedation following his long stay in PICU, and oral feeding was withheld. This inevitably delayed any investigation to confirm a safe swallow, and therefore NGT feeding was required to continue until formal video-fluroscopy was able to be performed. Following this, oral feeds were reintroduced, and he was eventually discharged home on postoperative day 66 feeding via bottle and with a nasogastric tube in situ for required top-ups to achieve 120ml/kg/day of high-energy formula. His discharge weight demonstrated an overall weight increase of 1.3kg from time of surgery.

Neonate 13 was known to have intrauterine growth retardation but was born at term at an appropriate size for gestational age, and within a normal weight-for-age z-score category. Following neonatal collapse at his local hospital on day 16 of life with absent femoral pulses, he was resuscitated, intubated, ventilated and commenced on prostaglandin infusion at 100 nanograms/kg/minute. Antibiotics were also started due to a history of a positive Group B

Streptococcal swab during pregnancy. He was transferred to the intensive care unit at the study hospital where his cardiac diagnosis was confirmed as hypoplastic aortic arch with VSD. Admission PIM2 score was 12%, and formal preoperative screening for methicillin sensitive Staphylococcus aureus was not performed, although a throat swab taken on ICU admission was positive and suggestive of colonisation.

Due to a diagnosis of maternal thrombocytopenia he received a preoperative Haematology consultation, although no treatment was required. He stabilised following medical management and prostaglandin was weaned to 10 nanograms/kg/min, with preoperative oxygen saturations of 98% in room air. Enteral feeds via nasogastric tube at a volume of 125ml/kg/day were administered. Onodera's PNI was the lowest in the sample, at 32.

Surgical risk was 2.3% and his operation was performed on day 22 of life, with weight remaining in a normal WAZ category. On return to intensive care, maximum inotrope score was 15 on operation day, and maximum oxygenation index was 6.5. Feeds were started 5 hours after ICU admission as lactates had decreased under 2mmol/L.

Delayed sternal closure occurred uneventfully on postoperative day 4, with drain removal occurring on postoperative day 7. Despite early progress and establishing enteral feeding at a volume of 75ml/kg/day, he was slow to wean from the ventilator with an increased effort of breathing. A bronchoscopy was performed on postoperative day 8 to check airway patency, but no trachea-bronchomalacia was identified. Following a gradual wean in ventilation over the following day, extubation occurred on postoperative day 10 and although initially he appeared to be coping well with spontaneous respiration, over the following hours his work of breathing increased with a raised lactate on arterial blood gas analysis. Consequently, he was electively reintubated on postoperative day 11, with concerns regarding possible necrotising enterocolitis (NEC) as a cause for the elevated serum lactate. Following review by the general surgeons, despite the absence of sound clinical or radiological features, he was put nil by mouth and conservative treatment for NEC commenced for a period of 7 days. Full parenteral nutrition was started on postoperative day 12, providing 103 kcal/kg/day, and although trophic feeds had been commenced on postoperative day 18, parenteral nutrition continued until full enteral feeds were re-established on postoperative day 25. At this time, no postoperative weight gain had been achieved.

Concerns of possible pulmonary over-circulation were raised due to ongoing cachexia and work of breathing limiting ventilation weaning, despite echocardiogram demonstrating adequate pulmonary artery band velocity. Following discussion at the joint cardiac meeting, it was agreed that a cardiac catheter would definitively answer this question, and he was listed for investigation.

Unfortunately, on postoperative day 29, a Staphylococcus aureus ventilator-associated pneumonia was diagnosed which delayed his cardiac investigation. A course of antibiotics was commenced, and ventilatory support was continued. However, nutritionally progress was seen with gradual weight increases observed following a change to high energy milk and feeding volumes at 120ml/kg/day.

Finally, on postoperative day 31, cardiac catheterisation demonstrated a lung blood flow four times higher than systemic, and he was re-listed for tightening of his pulmonary artery band. This occurred on postoperative day 34. He required no additional inotropic support following

surgery, and his mediastinal drain was removed the following day. He received routine post cardiac surgical antibiotic prophylaxis, and full feeds were re-established the following day. Subsequently, he began to make strides with ventilation weaning, and on low ventilator settings he had a repeat bronchoscopy on postoperative day 41 which was normal, and ventilation weaning had been commenced at cessation of follow up.

16d: Neonates with no enteral feeding

Neonate 2 was an antenatal diagnosis of pulmonary atresia with intact ventricular septum and subsequent hypoplastic right heart. He born in good condition and stabilised on a prostaglandin infusion in his local neonatal unit. Initially he was spontaneously breathing, but due to increasing oxygen desaturations required increasing prostaglandin doses, and he was electively intubated and transferred to PICU at 2 weeks of age for cardiology assessment and further management. Although following transfer he was weaned from mechanical ventilation and successfully extubated, once again decreasing oxygen saturations led to the need to reintubate, with the decision to proceed to interventional cardiac catheterisation and stenting of the ductus arteriosus to maintain adequate oxygen saturations.

Enteral feeds during this time reached a maximum volume of 83ml/kg/day, with a weight increase of 510g from birth to the time of the procedure. Although at birth he was in a low (underweight) WAZ category, his size was appropriate for gestational age and by the time of surgery at 18 days of age, he had reached a normal WAZ category. His preoperative Staphylococcus aureus status was negative.

During attempted ductal stenting, there was significant haemodynamic collapse requiring immediate transfer to the operating theatre for an emergency BT shunt which was performed on cardiopulmonary bypass with an operative risk of 27%. He returned to the intensive care unit postoperatively in a critical condition on inotropic support and with his chest wall left open. Risk of death on PICU admission was predicted at 5%.

He was bleeding at 45ml/kg (2ml/kg/hr) and required 190ml/kg of fluid administration (blood/blood products/ drugs) during his first day on PICU. Despite this, there was continued deterioration, with a maximum inotrope score rising to 65 on postoperative day 3. Oxygenation index had also deteriorated to 22.7 from an admission index of 5.

There were a number of attempts to close the chest, but baby did not tolerate them, becoming haemodynamically unstable. He remained fragile and in critical condition. He became anuric and commenced peritoneal dialysis for acute kidney injury. Due to persistently elevated lactates enteral feeding was unable to be commenced and therefore he commenced parenteral nutrition on day 10. Due to his precarious position and failure to progress, a multidisciplinary decision was made for a cardiac catheter and balloon atrial septostomy. This was performed on postoperative day 15, with baby developing hypoxic bradycardic arrests unresponsive to resuscitation. Resuscitation attempts were discontinued in the cardiac catheterisation laboratory.

Neonate 7 was born at 38-weeks' gestation in good condition and discharged home on day 1 of life. He presented to his local hospital on day 3 of life with poor feeding and neonatal jaundice. Initially stable, by the following morning his condition had deteriorated with poor perfusion, respiratory distress and severe lactic acidosis with poor femoral pulses. He was

intubated and ventilated and commenced on antibiotics and prostaglandin infusion. He was hypothermic, coagulopathic with evidence of acute kidney injury. Inotropic support was added, and he was transferred to the intensive care unit at the study hospital. His PIM2 score was 27% at the time of admission.

Echocardiogram confirmed a diagnosis of hypoplastic left heart syndrome. Over the following days with intensive care support, end organ function gradually improved. Once lactate levels were normalised, enteral feeds were attempted but there were early concerns regarding possible NEC, despite the absence of radiological signs, in addition to ongoing concerns regarding sepsis despite antibiotic therapy. Admission surveillance swabs were noted to be positive for an extended-spectrum beta-lactam producing Enterobacter coli in tracheal aspirates, for which appropriate antibiotic therapy was given. He was MRSA negative, but methicillin sensitive Staphylococcus aureus swabs were not performed. Surgery was postponed twice to optimise his condition. Finally, at 19 days of age, stable on a prostaglandin infusion at 20 nanogram/kg/min, and with a nutritional index of 69.7, he underwent Norwood Sano operation with predicted mortality at 32.6%.

After an initial 48 hours of relative stability, with a maximum inotrope score of 19 and oxygenation index of 15, there was an acute clinical deterioration with hypotension, worsening gas exchange and acidosis. The baby was started on antibiotics for presumed sepsis, and although abdominal x-ray did not show evidence of bowel perforation or NEC, a general surgical review was requested. However, with continued deterioration the baby required the institution of extra-corporeal mechanical support with evidence of overwhelming sepsis. Blood cultures taken the following day grew E. coli ESBL. Despite full mechanical support, and renal replacement therapy in the form of haemofiltration, serum lactates remained grossly elevated. The baby was kept nil by mouth and commenced parenteral nutrition on postoperative day 8, and 108ml/kg/day were able to be achieved on full TPN. Cranial ultrasound scans showed evidence of ischaemia but no intracranial haemorrhage, which would be a contra-indication to continuing mechanical support. Abdominal ultrasound demonstrated a splenic infarct but no evidence of perforation or collections.

Following some improvement in the baby's overall condition, an attempt to wean from mechanical support was undertaken on postoperative day 10. However, after 20 minutes off ECMO there was clinical evidence of hypoxia, bradycardia and hypotension, therefore ECMO support was continued. After a further 5 days of mechanical support, arrhythmia was noted and treated medically. On day 14 of ECMO (postoperative day 16), a second wean was undertaken and decannulation occurred. However, clinical instability led to ECMO being re-instituted, and there were ongoing problems with bleeding.

Following further discussion with the general surgeons, and with failure of the baby to progress clinically, a high-risk laparotomy was undertaken on ECMO support on postoperative day 17. Following evidence of jejunal ischaemia and perforation, excision and formation of stomas was performed. Postoperatively there was subsequent clinical deterioration, with multi-system organ failure. Although it was felt there was ongoing abdominal sepsis, the consensus view was that repeat laparotomy would be difficult and prove fatal. After some clinical improvement in clinical parameters whilst on ECMO, on postoperative day 31 a final attempt to separate from mechanical support was attempted and failed, therefore the gravity

of the situation was discussed with the baby's parents and a decision to withdraw active treatment was made.

Appendix 17: Plans for study dissemination

Publication of research findings

Previous publication:

Hill et al (2016) Is undernutrition prognostic of infection-related complications in children after surgery? Journal of Hospital Infection, 93, pp. 12-21

Future publications are planned for:

1. Paper presenting findings regarding barriers to neonatal feeding after surgery in cardiac neonates whilst on intensive care, to be targeted at Pediatric Critical Care medicine (Impact Factor 3.495).
2. Paper presenting the identified patterns of neonatal feeding after cardiac surgery in neonates, to be targeted at Journal of Nutrition (Impact Factor 3.42).
3. Paper presenting MSSA carriage in a paediatric cardiac surgical population to be targeted at Journal of Hospital Infection (Impact factor 3.126)

Presentation of research findings

Previous conference presentation:

Is undernutrition prognostic of infection-related complications in children after surgery? RCPCH, Birmingham, April 2016

Future conferences will be targeted with abstracts for oral presentation being submitted to:

1. "Enteral feeding patterns in neonates following cardiac surgery", BCCA conference, November 2018, Liverpool
2. "Barriers to enteral feeding neonates after cardiac surgery", PCICS conference, San Diego, California, September 2019 (or similar)

Study findings will be presented locally within the study hospital at the following meetings:

1. Joint Cardiology and Cardiac Surgical Quality Assurance and Quality Improvement Meeting

2. Consultant Meeting Intensive Care Unit

3. Grand Round

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Review

Is undernutrition prognostic of infection complications in children undergoing surgery? A systematic review

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SUMMARY

Background: Healthcare-associated infections are costly and are increasingly viewed as an indicator of the quality of care. Although strategies to reduce infections have become widespread, few studies have formally investigated the role of undernutrition on the development of infection-related complications in children after surgery.

Aim: To perform a systematic review of the literature to determine if undernutrition is prognostic of postoperative infection complications in children.

Methods: Electronic bibliographic and research databases were searched from 1950 to 2014. Inclusion criteria were studies in children (age <18 years) evaluating pre-operative nutritional status and reporting postoperative infection complications. Quality assessment was performed independently by two reviewers, with disagreements resolved by a third reviewer. The quality of the evidence was judged to be low in the majority of studies.

Findings: Ten cohort and two case–control studies met the inclusion criteria. Five studies reported an outcome combining infection-related complications, with the remainder reporting individual infection complications. Six studies reported surgical site infection (SSI) alone or in combination with other infection complications. Direct comparison between studies was difficult due to clinical and diagnostic heterogeneity. Unadjusted analyses (for patient or clinical variables) were suggestive of a relationship between undernutrition and infection complications. In studies controlling for other variables, the analyses did not remain significant for SSI.

Conclusion: There was low-quality evidence that undernutrition may be predictive of postoperative infection complications in children, with the exception of SSI. However, inconsistencies in nutritional and outcome assessments made it difficult to draw conclusions. Larger, high-quality studies are warranted to further investigate a potential prognostic relationship.

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