UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE

Human Development and Health

Quality, Clinical Outcomes and Treatment Costs in Acute Intestinal Failure

by

John Alexander Saunders

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ABSTRACT

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Type 1 and type 2 intestinal failure (IF) are associated with significant morbidity and mortality, with little published data reporting outcomes from clinical practice. This thesis will therefore examine the definitions, quality of care, clinical outcomes and treatment costs of these conditions within the setting of an acute hospital which cares for many type 1 IF patients as well as running a regional intestinal failure service for type 2 and 3 IF patients.

Observational studies were conducted to examine; the parenteral nutrition (PN) care provided to patients with all types of IF, screening tools and criteria to identify type 2 IF in clinical practice and an assessment of clinical outcomes and treatments costs in this complex patient group.

The multidisciplinary nutrition and intestinal failure team were involved in 90% of decisions regarding initiation of PN in this hospital compared to only 52.7% reported by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report. Standards of assessment, monitoring and catheter complications were also better than those in the NCEPOD report. Rates of catheter related sepsis were lower in patients managed within a specialised IF unit compared to other wards; 1.8 episodes/1000 PN days versus 8.21 episodes/1000 PN days ($p<0.0001$). The requirement for PN for >28 days had a 91% sensitivity and 96% specificity for identifying type 2 IF but a low positive predictive value of only 59%. IF surgery criteria had a sensitivity of 96% and a positive predictive value of 100% for identifying type 2 IF.

Mortality during an acute admission for type 2 IF patients (n=44) was 4.2%. Following reconstructive surgery (n=37) there were no post-operative deaths, no readmissions within 30 days and only one post-operative fistula recurrence. After surgery 94% of patients were independent of artificial nutrition. The median calculated treatment costs per day for patients with type 2 IF was £572. Current funding mechanisms within the NHS only allow hospitals to recover 44.7% of the treatment costs in type 2 IF.

These studies confirm that standards of PN care in IF can be high within a regional specialist centre, with low rates of mortality, fistulae recurrence and PN dependence in type 2 IF. Criteria for screening and defining type 2 IF are relevant to clinical practices and their wider use could result in earlier access to specialist treatment, improvements in outcome reporting and a mechanism for establishing future IF funding.

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DECLARATION OF AUTHORSHIP

I, John Alexander Saunders declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

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I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. Parts of this work have been published as:

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Signed: .....

Date: .....

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Definitions and Abbreviations

BANS	British Artificial Nutrition Survey
BAPEN	British Association of Parenteral and Enteral Nutrition
BMI	Body Mass Index
CABSI	Catheter associated blood stream infection
CRBSI	Catheter related blood stream infection
CRS	Catheter related sepsis
CSBSI	Catheter suspected blood stream infection
CT	Computerised tomography
CVC	Central venous catheter
DVT	Deep vein thrombosis
ECF	Enterocutaneous fistulae
ESPEN	European Society for Clinical Nutrition and Metabolism
ETF	Enteral tube feeding
HIFNET	Home Intestinal Failure Network
HPN	Home parenteral nutrition
ICD	International classification of disease
IF	Intestinal failure
IFALD	Intestinal failure associated liver disease
IFU	Intestinal failure unit
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NPWT	Negative pressure wound therapy
NST	Nutrition support team
ONS	Oral nutritional supplements
PbR	Payment by results
PICC	Peripherally inserted central catheter
PN	Parenteral nutrition
SBS	Short bowel syndrome
UHS	University Hospital Southampton NHS Foundation Trust

Chapter 1: Introduction

1.1 Background

Intestinal failure (IF) is characterised by a reduction in gut function resulting in an inability to maintain macronutrient and or water and electrolyte balance(1). For many years the term IF has been synonymous with chronic irreversible conditions with a requirement for long-term home parenteral nutrition (HPN) (1). In the United Kingdom over the last decade the definition of IF has evolved, the term used in a broader context to include all patients who require parenteral nutrition (PN) in an acute or chronic setting (2, 3). A sub classification has been applied, which more recently has gained wider support from European experts (4).

As a consequence of this change, IF is now considered as a spectrum of disease that has a wide variety of aetiologies, severity, chronicity and a variable need for medical support. Patients with IF largely fall into one of three clinical categories (see table 1.1, adapted from Shaffer and Lal (2, 3)). Patients with type 1 and 2 IF have an acute onset, short or medium term problem that is potentially reversible. There is a considerable degree of overlap between the two categories and at presentation it may be difficult to distinguish between them. Within this thesis the term 'acute IF' will therefore be used when issues pertinent to both subtypes are discussed together. Those with type 3 IF have chronic conditions and little chance of achieving nutritional independence. This classification aims to outline the likely management and expertise required as well as organisational issues in the treatment of IF.

Table 1.1 Sub classification of intestinal failure

IF subtype	Description
1	A self-limiting condition frequently occurring in the perioperative and critical care settings. Commonly managed in non-specialist units on general surgical wards and critical care units in conjunction with a multidisciplinary nutrition support team (NST). Patients receive parenteral nutrition support for a limited time before making a full recovery without complication.
2	An uncommon condition in severely ill patients with major resections of the bowel and septic, metabolic and nutritional complications requiring multidisciplinary intervention with metabolic and nutritional support to permit recovery.
3	A chronic condition in metabolically stable patients requiring long term home parenteral nutrition often for years, with need for careful monitoring for complications.

Proposed by Lal (3)

Type 1 IF is the most common presentation of IF, it follows an acute reversible cause requiring PN support for a number of days or a few weeks. These patients are predominantly managed on surgical wards and intensive care units in acute hospitals. The prevalence is relatively low but most acute hospitals will treat a number of patients at any given time point. However, despite this almost universal clinical activity, there are few published data regarding outcomes, complications or indicators of the quality of PN care.

There is increased recognition that type 2 IF is a specific disease entity that presents unique challenges and is best managed by specialist units. In England it also poses specific difficulties with respect to how services are provided and funded both locally and nationally (5). The true incidence of type 2 IF is unknown which is in part due to the lack of objective diagnostic criteria. Estimates suggest that the number of patients is actually very small, 5.5-9 new patients per million of population per annum in England (5, 6). However, there is no national system in place for recording levels of clinical activity and anecdotally there have been suggestions that many institutions are undertaking a small but significant amount of work.

Type 3 IF is characterised by a long term requirement for HPN in patients who are clinically stable in an outpatient setting. In the UK patients are usually managed by specialist units in conjunction with commercial home care companies. There is a voluntary national registry for patients receiving HPN, although not all patients are captured through this system. Data reported from 2007 and 2011 estimate that between 10-14.5 patients per million receive HPN in the UK (7). The management and issues relating to type 3 IF fall outside the scope of this body of work.

For many years national and international professional bodies such as the British Association of Parenteral and Enteral Nutrition (BAPEN), the National Institute for Health and Care Excellence (NICE) and the European Society for Clinical Nutrition and Metabolism (ESPEN) have called for improved standards of care in patients at risk of malnutrition, including those receiving PN (8). In acute IF there are no universally agreed quality indicators and it is potentially difficult to establish what these should be. This is a consequence of a combination of factors which include; little published outcome data, diverse patient cohorts, small incidence of IF cases and considerable variation in how these services are provided across the UK.

1.2 Outline of thesis

1.2.1 Quality of care in acute intestinal failure

Until recently little published data existed regarding the quality of care in acute IF. In 2010 following a national retrospective observational study examining the PN care received by 877 patients, the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) published a detailed report demonstrating significant deficiencies in the care provided in many institutions. Overall it was judged that only 19% of patients received a level of care that represented a good standard of practice.

It is well recognised in many fields of medicine that increased specialisation and the development of specialist teams and units results in improvements to clinical outcomes. However whether the same is true in acute IF is unknown. This thesis will prospectively examine the PN care provided to patients with acute IF in a single specialist centre with regard to nutritional assessment and monitoring. It will also assess whether the standards of care are higher on a dedicated intestinal failure unit (IFU) with regard to catheter related sepsis (CRS) and accuracy of PN administration.

1.2.2 Validity of criteria for diagnosing type 2 intestinal failure and intestinal failure surgery

There are currently no universally agreed criteria to determine which patients should be referred to specialist IF centres. In part this is due to differing clinical interpretations of the definition of type 2 IF. This is compounded by the current lack of infrastructure with insufficient capacity within the National Health Service (NHS) to accommodate all referrals. Historically, expert opinion has suggested that all patients receiving PN for longer than 28-35 days should be discussed with an IF centre, although, there is little published evidence for this approach (3).

Due to the significant heterogeneity of the patients with type 2 IF, guidance has been issued to help clarify in which clinical settings an operation should be designated a type 2 IF procedure. This thesis will examine the reproducibility of these criteria and apply them to a historical database of patients with type 2 IF to ascertain the utility of their application in clinical practice. It will also allow an assessment as to whether a surrogate marker such as duration of PN requirement is an appropriate screening tool for assessing acute IF.

1.2.3 Clinical outcomes in patients with type 2 intestinal failure

There is very little published literature with regard to the outcomes of patients with type 2 IF. However, there is a wider evidence base from centres regarding clinical outcomes following surgery for complex enterocutaneous fistulae (ECF). This is a potentially useful comparator as it is thought that a high proportion of patients with type 2 IF have complex ECF and parallels can potentially be made.

This thesis will examine the outcomes of a cohort of patients with type 2 IF managed in a regional IF referral centre to develop an understanding of the incidence, aetiology and clinical outcomes as well as to identify potential quality indicators that may result in improvements in standards of care in the future.

1.2.4 Treatment costs of managing patients with type 2 intestinal failure

Much of the published data on type 2 IF and documents relating to potential configuration of IF services describe long complex admissions, often with significant stays in critical care and input from multiple specialist teams. This inevitability makes the management of this cohort of patients very costly to individual institutions but the current tariff structure within the NHS does not incorporate a costing code for IF and so hospitals which manage these patients may potentially develop a significant shortfall in income. This thesis will examine the potential cost drivers for

patients with type 2 IF and consider how the provision of these services could be funded in the future to ensure adequate resources are available to provide the quality of care that is required.

1.2.5 Summary

This thesis will examine the following areas to characterise the quality of care provided to patients with acute IF, report outcome measures, assess potential quality indicators, review criteria for classifying IF and consider the cost implications for providing such services:

1. Assessment of the quality of care provided to a cohort of patients with acute IF in a regional centre and evaluate whether a dedicated IFU improves clinical outcomes.

2. Assessment of the validity of duration of PN treatment as a screening tool for identifying cases of type 2 IF and gauging the utility of the proposed criteria for type 2 IF surgery to capture clinical activity.

3. Examining the clinical outcomes of a cohort of patients with type 2 IF from a single regional centre and identification of potential quality indicators.

4. Identifying the costs of treating patients with type 2 IF.

Chapter 2: Literature Review

2.1 Defining intestinal failure

Historically the term IF has been used to describe a range of patients in a variety of clinical settings. Although attempts have been made to reach a consensus regarding what constitutes IF, it still lacks a universally accepted definition. In part this is due to the use of the term *failure,* which in most medical specialities is widely considered to include patients with partial loss of organ function. Applying this principle in IF would potentially create a spectrum of severity, with less severe IF patients meeting their nutritional requirements with additional oral and enteral treatments through to more severe patients dependent on parenteral support.

A broader definition including patients with only partial loss of function not only increases the apparent disease prevalence but also makes categorising and recording data much more challenging due to the widespread occurrence of malnutrition and nutritional interventions in clinical practice. Therefore for the purposes of this thesis, the term IF will only include those patients who have a dependency on parenteral support. This is largely in keeping with current UK clinical practice and recent European consensus, although it is acknowledged that there is a cohort of patients with nutritional deficiencies which occur as a result of insufficient absorption that are managed by clinicians with an interest in nutrition which is beyond the scope of this body of work.

The term IF was first used by Fleming and Remington who defined it as “a reduction in the functioning gut mass below the minimum amount necessary for adequate digestion and absorption of food” (9). Since that time a number of definitions have been proposed to take into account essential requirements other than macronutrients (10). More recently in response to developments in surgery, drug therapy and advances in intestinal transplantation the definition has evolved and the following is often used “a reduction of gut function below the minimum necessary for absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth” (4).

Many patients with IF have short bowel syndrome (SBS) and in this group, attempts have been made to predict the requirement for long term HPN based on the anatomical length of remaining small bowel and the presence or absence of a functioning colon. Data from a number of studies have shown a reasonable degree of consistency in demonstrating PN independence can be achieved in patients with >60cm of small bowel in patients with a jejunocolonic anastomosis and in >115cm of small bowel in those with end jejunostomies (11-13). Therefore these anatomical

lengths have been used by some authors to 'define' intestinal failure, although in clinical practice they serve more as guide to likely prognosis rather than as absolutes.

Anatomical length and presence of a colon are not the only factors that predict the development of IF. The presence of disease and the functionality of the remnant bowel are also factors, particularly relevant in Crohn's disease, one of the commonest causes of IF (3). Fasting plasma citrulline has been used as a measure of functioning enterocyte mass. Data suggests citrulline levels <5µmol/l predicts a dependence on HPN and therefore may also be considered to define IF in the chronic setting (14).

To date, the definition by Pironi et al combined with the functional classification originally described by Lal are the most practical in clinical practice (3, 4).

2.2 Acute intestinal failure

2.2.1 Type 1 intestinal failure

2.2.1.1 Definition

Type 1 IF occurs in hospitalised patients and is usually a consequence of an acute pathological event. It is most commonly seen in patients having undergone major abdominal surgery but is also seen in those with critical illness following pneumonia, head injury and acute pancreatitis. It is commonly caused by a prolonged ileus, it can also result from obstruction of the gastrointestinal tracts or alternatively, interruption to complete enteral continuity (perforation). Therefore patients need PN in the short term as a bridge to restoration of normal gastrointestinal function.

Whilst there is no universally agreed definition for type 1 IF, expert opinion agrees that it is a short term clinical problem. The duration of PN requirement is counted in days rather than weeks and it is this length of treatment that is increasingly being used to define the condition, although this is not evidence based. The vast majority of these patients require PN for less than 14 days and their ability to resume oral intake reflects improvements or resolution of the underlying condition. A proportion of patients with more serious complications or worse premorbid physical function may require a more prolonged course of PN.

2.2.1.2 Incidence of type 1 intestinal failure

There are no precise figures that indicate the exact incidence of type 1 IF. Most acute hospitals will treat this cohort of patients, particularly those undertaking abdominal surgery and therefore

it must be considered as a standard therapy. However without a precise definition which has utility in clinical practice or a mechanism to record these data it is unlikely that the scale of the problem will be identified.

Findings from the UK wide NCEPOD enquiry in 2010 help provide an estimate of current clinical activity. They identified 5527 patients of all ages in 218 hospital were issued with a prescription for inpatient PN during a 3 month period(15). Whilst this includes a proportion of patients who were hospitalised with type 2 or 3 IF and those who were is issued with a prescription and did not go on to receive the drug, it does indicate the volume of work undertaken in UK hospitals. This however may be an underestimate as not all hospitals made a return for the survey and it is based on recorded episodes only.

These data give an estimate of activity undertaken in the UK but has significant limitations and there will be considerable local variations in the number of patients treated with type 1 IF. Large university hospitals providing acute care for local populations and specialist regional services are likely to have a higher incidence of type 1 IF. In part due to the higher volumes of patients treated and those undergoing more complex surgery such as pancreatic or oesophagogastric are thought more likely to have complications requiring short term PN support.

2.2.1.3 Indications for parenteral nutrition and aetiology of type 1 intestinal failure

There are few published series reporting the aetiology of type 1 IF. Inevitably centres with sufficiently high use of PN to make reliable statements on incidence and trends in underlying aetiology will be larger regional hospitals often offering tertiary services and therefore are unlikely to be representative of nationwide patient demographics. Smaller hospitals will have relatively few cases of acute IF and therefore establishing a reliable reflection of aetiology may also have limitations.

Data from the 2010 NCEPOD report illustrate the underlying indication for PN from nationwide clinical practice (table 2.1) (15). Several of the categories have indistinct definitions such as “Crohn’s” or “post-surgical complications”. These broad terms reflect the limitations of retrospective observational studies and suggest there may also be a degree of overlap in some categories.

Table 2.1 Documented indications for PN treatment reported in NCEPOD study

Documented indication for PN	**Number of patients**
Post-operative ileus	195
Post-surgical complications	124
Obstruction	119
Non-functioning gut	109
Failure of enteral nutrition	109
Perforation/leaking gut	91
Fistulae	48
No enteral access	45
Cancer	30
Dysphagia	25
Malabsorption	23
Short bowel	22
Infection	20
Crohn's	15
Other	122
Not documented	73

(Answers may be multiple)

Despite the limitations, NCEPOD data describe the population of hospitalised patients treated with PN. The majority of the indications for PN appear to be the result of complications from surgery or intestinal pathology. There are a number of alternative causes of IF which are probably too small to categorise but demonstrate the diverse nature of the clinical scenarios encountered by hospital nutrition teams.

2.2.1.3.1 Postoperative ileus

As postoperative ileus is the single commonest identifiable indication for PN it will be discussed in further detail. It is has no universally accepted definition but is characterised by a transient cessation of bowel function after surgical intervention, which prevents the effective transit of intestinal contents and/or tolerance of oral intake (16). It is thought to occur in the majority of patients undergoing abdominal surgery with recovery in function usually occurring on day 3-5 following laparoscopic surgery or laparotomy.

It is thought that approximately 17% of patients develop a prolonged postoperative ileus (17). Patients develop abdominal distension, nausea, vomiting and delayed passage of stool and are unable to tolerate an oral diet. It is associated with increased complications including nosocomial infections, poor wound healing, anastomotic leaks and higher rates of relaparotomy. It is also associated with a significant increase in length of stay 13.8 v 8.9 days ($P<0.001$) (17). Postoperative ileus is thought to result from a combination of activation of sympathetic inhibitory neural pathways, administration of opioid analgesia, hormonal mechanisms, a proinflammatory response to bowel manipulation and over administration of IV fluids or persisting infection (18).

Enhanced recovery programmes have become standardised practice in elective surgery and have undoubtedly reduced the time to restoration of GI function and length of stay (19). Despite this there are still significant numbers of patients who develop prolonged postoperative ileus, it is thought that this is due to an increase in the technical difficulty of surgery, a rise due to the total number operations that are performed and the increasing age and comorbidities of those undergoing surgery. Therefore postoperative ileus is likely to remain a significant cause of type 1 IF in the future.

2.2.2 Type 2 intestinal failure

2.2.2.1 Definition

As with other forms of intestinal failure consensus definitions regarding sub classification have only recently become more widely accepted outside of specialist centres in the UK (4). It represents the more severe end of the spectrum of acute intestinal failure. It occurs in hospitalised patients who have a single unifying feature; severely ill patients with major resections of the bowel and septic, metabolic and nutritional complications requiring multidisciplinary intervention with metabolic and nutritional support to permit recovery (3).

The majority of patients with type 2 IF have had some form of intra-abdominal catastrophe, either as an acute primary event, such as acute mesenteric ischaemia or secondary to complications

from intestinal surgery. It is commonly associated with intra-abdominal sepsis, multiple organ dysfunction syndrome and metabolic instability.

Patients often have coexisting complex abdominal wounds, laparostomy wounds and enterocutaneous fistulae and may also have difficult intravenous access, intravenous catheter complications, severe myopathy secondary to acute illness, complications of drug therapy and psychological problems. The management of these complex patients requires a multi-professional specialist team and they often spend significant time in critical care.

Patients require a prolonged period of stabilisation and a proportion require surgical intervention during this time. Patients receive PN for many weeks and some patients with type 2 IF require a period of HPN whilst the acute intra-abdominal inflammation resolves, prior to consideration of further complex reconstructive surgery, often some months later.

In the UK attempts have been made to develop a national infrastructure for the provision of IF services (discussed further in section 2.4). In order to plan levels of service provision a definition of IF is required in order to identify patients who should be treated in specialist centres. Within the definition of type 2 IF used in this service development there were 4 subcategories of type 2 IF, one 'medical' and 3 'surgical' (20).

1) PN with complications or PN whose duration is causing concern.
2) Intra-abdominal sepsis, fistulation and/or open abdomen (laparostomy).
3) Patients requiring intestinal reconstruction.
4) Surgical re-appraisal.

The 'medical' subcategory, PN with complications or PN whose duration is causing concern, was then divided further into six subgroups.

a) Needing or expected to need PN for ≥28 days (discuss at day 14).
b) Requiring continued PN and have had >2 catheter infections.
c) Uncontrolled high output stoma despite standard management.
d) Patients with catheter-related central venous thromboses leading to problems of access for PN administration.
e) Medical management patients with persistent or deteriorating metabolic complications (significant liver or renal dysfunction, recurrent acidosis, poorly controlled diabetes).
f) Requiring long term in-patient PN with severe psychiatric co-morbidity (including personality disorders), needing intensive liaison psychological medicine services.

This medical subcategory includes some complex patient groups who may benefit from the expertise available in specialist IF centres but yet may not necessarily fulfil the definition proposed by Lal (3). There has been no published evidence that type 2 IF is defined in isolation by PN duration, the number of catheter infections or central venous thromboses. Similarly high output stomas refractory to standard management, isolated medical management of metabolic complications and severe psychiatric co-morbidity, although all may be important components of IF, taken in isolation do not define type 2 IF as described in the published literature.

This medical subcategory may be important in determining how IF services and expertise are provided, particularly in the UK, but do not necessarily encapsulate the definition of type 2 IF described in the peer reviewed published literature. Therefore these criteria in isolation will not be taken to define type 2 IF in this body of work.

The descriptive nature of existing definitions indicates the heterogeneity of the patients and the clear difficulties in classifying patients. The subjective nature of the existing definitions is a potential barrier to identifying the incidence and collecting data from existing clinical practice. Therefore, in this study the definition of type 2 IF that will be used is the one first described by Lal (3).

2.2.2.2 Type 2 intestinal failure surgery definitions

Approximately 60% of patients referred for specialist IF management will undergo an attempt at reconstructive surgery (6). In recent proposals for UK IF service development, a panel of experts defined the types of operation considered to be a specialist intestinal failure surgical procedure or 'IF surgery' (see table 2.2)(20). Whilst this is not validated and based solely on expert opinion it does allow for inclusion of spectrum of patients felt to be reflective of clinical practice.

Enterocutaneous fistulation in specialist clinical practice is considered to be a frequent cause, if not the commonest cause, of type 2 IF. One author reports ECF account for 44% of type 2 IF cases, although this may appear an overestimate, there are little published data to refute this figure (21). However, there are a significant number of patients who still fulfil the narrative definition of type 2 IF without the presence of fistulae. This proposed classification of IF surgery may allow further audit and research into this evidence poor area with the potential to refine criteria and outcomes in the future.

Table 2.2 Definition of a specialised intestinal failure surgical procedure

1. Have had a prolonged period of parenteral nutritional support or enteroclysis (> 14 days) prior to abdominal operations. AND EITHER 2. Enteric fistulation associated with: a. Open abdomen (laparostomy); or b. Other intra-abdominal organs (i.e. upper or lower GI, urinary, gynaecological, hepato-pancreatico-biliary); or c. Abdominal sepsis requiring radiological or surgical drainage; or d. Significant co-morbidity - specifically: i. Collagen synthesis disorders such as Ehlers Danlos, Marfan's, and Pseudoxanthoma Elasticum; ii. radiation enteritis e. Recurrent fistulation following previous surgical attempts to repair OR 3. Hostile abdomen (without fistulation) associated with: a. Open abdomen (laparostomy); or b. Re-operation for adhesions/sclerosing peritonitis; or c. Abdominal sepsis requiring surgical drainage; or d. Significant co-morbidity - specifically: i. Collagen synthesis disorders such as Ehlers Danlos, Marfan's, and Pseudoxanthoma Elasticum; ii. radiation enteritis
4. Abdominal surgery where planned operative intervention would deliberately result in a period of intestinal failure (e.g. creation of a proximal jejunostomy).
5. Abdominal surgery where the primary aim of the surgery is to restore intestinal continuity allowing cessation of parenteral nutritional support, including HPN and fistuloclysis, and/or otherwise improve quality of life specific to intestinal failure.
6. Abdominal surgery requiring complex abdominal wall reconstruction (component separation, plastic surgical flaps, prosthetic implants, abdominal wall transplants)
7. Abdominal surgery for autologous GI reconstruction (tapering, lengthening, reversed loops STEP and Bianchi/LILT procedures) or intestinal transplantation.

2.2.2.3 Incidence of type 2 intestinal failure

There are a number of barriers that prevent the true incidence of type 2 IF being accurately reported. Firstly, with existing definitions requiring significant clinical interpretation, any differences between units could result in potential over and under reporting. Secondly, within the NHS there have been considerable variations in how these patients are managed, some institutions managing small numbers of type 2 IF patients whilst others referring to centres with regional expertise.

Accepting the above limitations, within the NHS efforts have been made to establish the clinical need on which to base specialist service provision for type 2 IF. Information gathered from an assessment of referral patterns in two specific geographical regions, combined with self-reported data from existing regional centres already undertaking this activity was used to provide an estimate of the incidence of new cases (5). The conclusion extrapolated for England estimated an incidence of type 2 IF of 9 cases per million of population, based on the definition of treatment for 28 days or more of PN.

Historical data estimate the incidence of 5.5 cases per million (6). However this likely represents an underestimate, as at that time considerably more patients were thought to be managed in non-specialist centres. More recent data from the same institution report 134 referrals between 2002-2005, with some regions referring up to 8.1/million patients (3).

2.2.2.4 Aetiology of type 2 intestinal failure

The commonest cause of type 2 IF results from complications following abdominal surgery. Data from one national centre demonstrate that surgical complications accounted for 42% of cases, the remaining aetiology being made up from Crohn's disease 21%, ischaemia 16%, dysmotility 11%, radiation 3%, malignancy 2% and other 5% (22).

Over the last few decade's there has been a steady increase in the frequency of cases of type 2 IF occurring as a result of surgical complications according to expert opinion. 70% of type 2 IF cases occur as a result of sepsis and fistulation usually following abdominal surgery for malignancy, inflammatory bowel disease or division of dense adhesions during relaparotomy (23, 24). Although not well characterised it is thought that these changes have occurred as a result of a combination of factors which include; increased complexity of surgery, increased patient age and comorbidities in those undergoing surgery.

2.3 Management of acute intestinal failure

Acute IF is a spectrum of disease. Therefore differentiating between type 1 and 2 patients may not be possible in the early stages and it is unlikely that distinction between the two will affect the initial clinical management. Therefore the management of both type 1 and type 2 patients will be discussed together.

2.3.1 Preventing intestinal failure

An important and frequently overlooked aspect of IF management is prevention. It is impossible to prevent all post-operative complications from occurring or indeed some patients progressing to develop more complex and irreversible forms of IF. However, there is evidence from a number sources which suggest better identification of high risk patients, improved perioperative management and better surgical techniques reduce specific intestinal and overall complications (25-27).

A number of generalised and specific pre-operative patient risk factors have been identified which are associated with increased risk of complications in many areas of colorectal surgical practice. In a study of 343 patients undergoing a total of 566 operations requiring an intestinal anastomosis for primary or recurrent Crohn's Yamamoto et al identified an increased risk of post-operative intra-abdominal septic complications (anastomotic leak, collection, or development of enterocutaneous fistulae) was significantly associated with preoperative albumin concentration <30g/l ($P<0.04$), preoperative steroid use ($P=0.03$), abscess at the time of laparotomy ($P=0.03$) and fistulae at the time of laparotomy ($P=0.04$), although the paper did not report the actual relative risks (28). A French study of 84,000 patients undergoing surgery for colorectal cancer identified the following variables were independently associated with increased 30 day mortality; age > 70 years, emergency surgery, presence of liver metastasis, malnutrition and the presence of respiratory, vascular or neurologic comorbidity (29).

There has been a continued focus to highlight the importance of optimisation in the pre-operative and perioperative setting in reducing preventable complications. Particular concern for a number of years has focused on emergency surgery with regard to the pre-operative fluid management, timing of surgery and post-operative recovery in critical care, all factors which can be potentially modified (27, 30).

Operative technique is also a significant factor in the development complications following abdominal surgery. In a retrospective study of 270 patients undergoing reoperation Van Der Krabben et al identified inadvertent enterotomy during relaparotomy occurs in 19% of cases (31).

They identified both patient age (OR 1.9 (CI 1.3-2.7); P<0.001) and having had 3 or more previous laparotomies (OR 10.4 (CI 5.0-21.6); P<0.001) were independently associated with inadvertent enterotomy. The occurrence of an inadvertent enterotomy was associated with a significant increase in the need for further urgent relaparotomies (P<0.001), critical care admission (P<0.001), PN use (P<0.001) and length of stay (P<0.001).

In a small retrospective study in 41 patients with type 3 IF resulting from Crohn's disease, Agwunobi et al identified that only 7 patients (17%) developed type 3 IF as a result of extensive primary disease (32). 9 patients (22%) developed type 3 IF after uncomplicated sequential resection, median of 3 (range 2-8) operations over a median of 17 (range 3-27) years. However, 25 (61%) patients developed type 3 IF after multiple (median 4, range 2-7) unplanned laparotomies for intraabdominal sepsis over a median of 0.5 (range 0.1-1.5) years. This suggests in Crohn's disease IF develops primarily as a result of complications of surgical treatment rather than extensive disease.

Better education to enable identification of high risk patients, high risk surgery and optimisation of those undergoing emergency surgery could result in the reduction in complications and therefore a reduction in the incidence of acute IF.

2.3.2 Systematic approach to management of acute intestinal failure

The adoption of a structured extended multidisciplinary approach to patient care has resulted in significant reductions in mortality and morbidity in specialist centres managing patients with type 2 IF. Historical data from Irving et al demonstrated improvements in mortality from 42% to 21% in the 1980's, with further significant reductions (7-11%) seen in more recent years (33-35).

The structure of the universally agreed approach is based around the management of sepsis and nutrition, along with the establishment of anatomy and careful planning, commonly referred to by the acronym of SNAP (see Table 2.3). The order of the sequence is important because each step will not be successfully accomplished until the preceding one is addressed and managed, however in practice often multiple steps are addressed simultaneously.

Table 2.3 The clinical approach to managing intestinal failure.

SNAP approach to intestinal failure	
Sepsis	• Cultures/swabs • Abdominal imaging • Radiological drainage • Other sources (respiratory tract, endocarditis)
Nutrition	• Dietary assessment • Supplemental feeding: enteral/ parenteral/ fistuloclysis
Anatomy	• Contrast studies to delineate origin of fistula and intestinal length • Endoscopy
Plan	• Multidisciplinary approach • Timing of surgery (Early for uncontrolled sepsis versus elective) • Metabolic and nutritional optimisation • Wound/stoma care • Treat underlying disease • Support and training where home nutrition required.

Adapted from Lal et al (3)

2.3.2.1 Sepsis

Successful management of abdominal sepsis is the most important determinant of outcome, particularly in type 2 IF. In case series reported by 3 specialist IF centres in the UK, of those who died sepsis was the direct cause in 75% (3/4), 77% (23/30) and 100% (4/4) of the patients (3, 34, 35). Data from 2 of these centres estimated that nearly all patients harboured some source of infection, with 42% of patients having intra-abdominal abscesses present on transfer from other hospitals (3, 34).

The cardinal features of sepsis in IF are frequently the same as non-IF settings. However, in type 2 IF, the complexity of disease and coexisting metabolic complications can result in a more insidious

presentation. This is especially true in the case of chronic abdominal sepsis from a walled off abscess, where patients may present with signs which may be easily overlooked such as hyponatraemia, hypoalbuminaemia, abnormal liver function tests or weight loss (21).

Primary abdominal sepsis often results in hypotension with consequential organ hypoperfusion and causes a cycle of sustained tissue damage through a positive feedback loop. Intestinal hypoperfusion results in the generation of proinflammatory mediators which in turn cause increased intestinal permeability, bacterial and endotoxin translocation and contribute to ileus (36, 37). This exacerbates tissue damage, and promotes secondary intestinal infection and multiple organ dysfunction.

Intra-abdominal abscess formation and ensuing complications are the hallmark of sepsis in the context of type 2 IF. The primary event results from a breach in the mucocutaneous barrier and subsequent translocation of intestinal flora into adjacent tissues. Animal models of abdominal sepsis have been used to identify bacterial factors and responses of the host defence important in the pathophysiology. Studies using intra-abdominal implantation of a faecal load have demonstrated a biphasic disease process, initially characterised by generalised peritonitis followed by abscess formation after 5 days (38).

When assessing outcome measures from sepsis of any cause a number of variables have been related to a worse prognosis. Host factors which have been associated with poor outcome include age, co-morbidity and functional status. The host's immune response to infection is also important, specifically the failure to generate a fever or the presence of leucopenia have been associated with increased mortality (39). Gastrointestinal sepsis is also associated with higher mortality rates compared to infection at other sites such as urinary tract or chest (40).

Nosocomial infections have a worse prognosis compared to those acquired in the community. The type of organism is also important, more resistant pathogens such as fungal and methicillin-resistant Staphylococcus aureus infections have been associated with significantly higher mortality (41). The response to treatment also predicts outcome with more significant improvements seen in those given antibiotics to which the organism is sensitive and in those whom tissue oxygenation is restored promptly (42).

2.3.2.2 Management of sepsis

Initial investigations follow standard clinical practice of blood and culture based testing from peripheral veins and any indwelling central catheters, urine cultures, wound swabs, including screening for methicillin-resistant Staphylococcus aureus. Frequently cross sectional abdominal imaging is required.

Radiological investigations will always be dictated by the clinical context, availability of technique and local expertise. However, computerised tomography (CT) is the imaging modality of choice in the context of suspected intra-abdominal sepsis in the post-operative patient. It has a diagnostic accuracy of >95% in abscess identification and has been shown in a number of studies to be superior to ultrasound or nuclear medicine techniques (43-45).

Source control is the term used to describe any action taken to limit the amount of infectious materials discharging from the primary site, usually referring to percutaneous radiological drainage of an intra-abdominal collection. In a multicentre prospective study of 96 patients treated with percutaneous drainage and intravenous antibiotics Cinat et al reported complete resolution of the infection with a single drain in 70% of patients, which increased to 82% with a second attempt (46). In this study only 53% of patients had a post-operative abscesses but this was independently associated with treatment success (P=0.04) (46). Inaccessible deep-seated collections may require an alternative radiological approach, such as trans-rectal or trans-vaginal drainage.

Patients who develop type 2 IF have often been shown to have abscesses which are difficult to manage and maybe refractory to drainage. A number of factors are associated with reduced success of percutaneous drainage (table2.4) (46-48). Techniques used in these situations include upsizing of drains, longer duration of treatment and fibrinolytic drugs instilled into cavities (49).

The complete resolution of an abscess may take several weeks, persistent high volume discharge raises suspicion of an entero-cavity fistula, which can affect up to 44% of all intra-abdominal abscesses (50). Prior to drain removal, especially those involving complex sepsis, further imaging is obtained to demonstrate collapse and resolution of the abscess. Sometimes in situations where the drain has a long course it will be withdrawn gradually over a period of several weeks.

Table 2.4 Factors associated with refractory abscesses

Underlying disease	Abscess associated with Crohn's disease Infected tumour
Anatomical	Presence of enterocutaneous fistulae Pancreatic collection Drainage route traverses bowel or pleura
Abscess related	Loculated abscess Presence of yeast Infected clot

Antimicrobial therapy has an important role in treatment of intra-abdominal sepsis. A number of studies have shown that primary antibiotic therapy was effective treatment without recourse to percutaneous drainage (51, 52). In a retrospective study assessing treatment for intra-abdominal abscess Kumar et el demonstrated that 54% (61/114) of patients improved on antibiotics alone, 44% required percutaneous drainage after incomplete response and 3% required surgery. However it must be noted that the abscesses in this study were uncomplicated. In acute IF, particularly type 2,it is more likely that patients have had more complex abdominal disease, previous antibiotic exposure, and prolonged hospitalisation and are therefore more likely to have had infection resulting from a nosocomial multi-resistant pathogen (53).

Despite advances in interventional radiology there are situations where further surgery is required. In patients with severe secondary peritonitis there are two surgical treatment strategies following initial emergency laparotomy, either planned relaparotomy or on-demand laparotomy. A randomised controlled trial demonstrated there were no significant differences between either treatment with regard to mortality. However, the on demand group had significantly fewer laparotomies, shorter ITU stays and shorter hospital stays (54).

In established type 2 IF most patients do not require further surgery, data from 2 UK IF centres reported that in patients with complex enterocutaneous fistula only 4% required surgery to control intra-abdominal sepsis (34, 35). Expert opinion suggests this is usually in the setting of impractical or ineffective radiological drainage, multiple interloop abscesses and complete anastomotic discontinuity (23). The two operations commonly performed are exteriorisation of fistulating intestine or proximal defunctioning stoma. Surgery also allows effective drainage of septic foci.(55)

Relaparotomies are technically demanding due to the presence of persistent intra-abdominal sepsis, intra-abdominal adhesions and the chance of inadvertent enterotomy. Adhesions occur as a consequence of trauma damaging the mesothelial cells which line the peritoneal cavity. Trauma results in a cascade of proinflammatory mediators and proteinaceous exudate, with high levels of fibrinogen. After surgery there is a reduction in equilibrating fibrinolytic mechanisms caused by a reduction in plasminogen activation (56). Animal studies have demonstrated plasminogen activating inhibitors are found in higher concentrations in damaged peritoneal tissue particularly in the context of infection and ischaemia. Disruption of the fibrinolytic process results in the ingrowth of fibroblasts and capillaries resulting in the formation of more connective tissue (57).

In patients with severe abdominal sepsis adequate source control may necessitate a decision to leave the abdomen open (laparostomy). This is usually performed in patients with extensive abdominal contamination resulting from fistulating disease where it is impossible to create a proximal defunctioning stoma, without risking further damage to normal intestine (25). In a study of 40 patients randomised to either a laparostomy or a standardised closed approach Robledo et al demonstrated no significant difference with regard to the development of acute renal failure, duration of ventilatory support, requirement for PN or need for need for re-operation due to residual infection (58). There was however a non-significant trend towards increased mortality in the laparostomy group, 55% versus 30% ($P>0.05$).

2.3.3 Nutrition support in the management of acute intestinal failure

Malnutrition is both an important cause and consequence of many different diseases and in many specialties, the presence of malnutrition is widely recognised as being associated with worse clinical outcomes (59). The importance of nutritional status has been widely recognised, with national recommendations that it be assessed on all patients admitted to hospital (8).

Malnutrition is particularly prevalent in gastrointestinal surgical patients, affecting between 43-58% of patients (60, 61). The cause is often multifactorial; reduced nutrient intake, impaired digestion and absorption, excess losses and alterations in nutrient processing all occur as a result of abdominal pathology and result in increased rates of malnutrition. Patients undergoing major abdominal surgery are subjected to huge physical insults, often resulting in further periods of reduced oral intake during the immediate post-operative period and consequent reductions in nutritional status.

2.3.3.1 General consequences of malnutrition

The consequences of malnutrition relate to its detrimental effects on tissue structure and physiological function. Sustained failure to meet nutritional demands results in a process termed reductive adaptation, a necessary response to preserve essential functions which is accompanied by an associated cost (62). The consequence of preserving vital functions is a reduction in the capacity for metabolic flexibility and decreased functional reserves, the absence of which is particularly important in the event of disease.

The most visible consequence of malnutrition is loss of weight and changes in physical appearance, a result of utilising reserves of muscle and fat as an energy source. There is relative preservation of more active visceral tissues, although if prolonged, major organs are also affected (62). However, it is not just changes in tissue structure that affect physiological function. In healthy individuals muscle power is proportional to muscle mass when assessed by hand grip dynamometry. Rapid reductions in power have been seen in acutely unwell individuals and conversely swift improvements in power have been described in others receiving nutritional support. These dynamic changes occur much more quickly than would be anticipated through changes in muscle mass volume alone, demonstrating the importance of nutrient provision (63).

Chronic malnutrition causes detrimental changes in intestinal blood flow, cell turnover, villous height and pancreatic exocrine function. Resulting in reduced digestion and absorption combined with changes in intestinal permeability (59). There are also effects on colonic function, reduced capacity to resorb water and electrolytes and changes in bacterial populations result in diarrhoea.

Changes in cardiopulmonary muscle function have also been described as a consequence of malnutrition. Respiratory muscle strength and maximal voluntary ventilation have been shown to be reduced by an average of 60% in patients who are malnourished. Significant reductions in diaphragmatic area and mass in malnourished individuals have also been demonstrated at post mortem (64, 65). This resultant weakness undoubtedly reduces the capacity to cope with the increased ventilatory requirements of acute pulmonary disease or sepsis.

Functional reductions in cardiac capacity are well described in chronically malnourished individuals such as in anorexia nervosa; slow pulse, increased circulation time and reductions in cardiac muscle mass. However, a small study in patients managed in critical care following major sepsis or trauma demonstrated left ventricular mass and function were preserved over a 21 day period despite reductions in total body nitrogen and total body potassium that occur during major catabolism (66). Whilst these study findings may initially be considered contradictory, it likely

simply reflects the ability for preferential preservation of essential tissues during a relatively short study period, an important component of the reductive adaptation process.

Protein energy malnutrition is associated with wide ranging reductions in immune function. Malnutrition has been shown to particularly affect cell-medicated immunity, phagocyte function, cytokine production, secretory antibody response and complement activity (67). These effects have been observed even when the severity of malnutrition is mild. Micronutrient deficiency also suppresses immune function, reducing the innate T-cell mediated response resulting in dysregulation of the host response. Vitamins C and E along with selenium, zinc and copper also have important roles in buffering damage from free radical production (68).

The acute-phase protein response is also altered in patients with protein energy malnutrition. The systemic inflammatory response and immune expansion lead to unusual amino acid demands, in patients with severe malnutrition there is only a partial acute-phase response (69). There is a reduction in the synthesis of pro-inflammatory mediators such as interleukin-1 and interleukin-6 and reduced availability of precursors for protein synthesis.

Impaired wound healing is an important consequence of malnutrition. There are significant delays in deposition of post-operative collagen in patients with protein energy malnutrition, this has been demonstrated in those who are mildly malnourished as well as patients with moderate-severe malnutrition (70). Maintenance of normal pre-operative food intake has been shown to have a greater influence on wound healing response than pre-operative absolute losses of either protein or fat stores (71). Both these studies indicate that wound healing is not purely dependent on body composition but also reflects recent nutritional intake.

2.3.3.2 Nutritional status and clinical outcomes in general surgical and other patient groups

Numerous studies across a spectrum of healthcare settings have documented an association between malnutrition and poor clinical outcome (59). Malnutrition has long been associated with an increased risk of complications in patients undergoing surgery, particularly with regard to infections, wound complications and anastomotic leaks (72).

A number of studies have assessed whether preoperative nutritional screening can identify malnourished patients at risk of developing post-operative complications. In a prospective study of 653 patients undergoing elective abdominal surgery, Kuppinger et al identified a significant increase in complications in patients with reduced food consumption immediately prior to hospital admission (73). In this particular study neither BMI nor weight loss provided a better prediction of risk. However, other authors have identified that a reduction in a number of

nutritional indices; percentage weight loss, arm muscle circumference and body weight compared to ideal weight, were associated with significant increases in complications (74-76).

Surgical site infections affect 2.6-3.2 % of procedures, in an analysis of more than 15,000 cases Malone et al identified that in multiple logistic regression analysis weight loss within 6 months and diabetes were the only pre-operative risk factors significantly associated with increased infection rates (77). Makela et al identified that malnutrition was one of 5 variables that included hypoalbuminaemia, anaemia, chronic lung disease and emergency procedure that were significantly associated with an increased risk of wound dehiscence after midline laparotomy (78).

Measurements of body composition have also been assessed to determine their utility in predicting clinical outcomes. Reductions in both pre-operative fat free mass and skeletal muscle mass were found to be associated with a more severe systemic inflammatory response syndrome following major vascular surgery (79). Tandon et al identified that sarcopaenia affects 41% of patients on the waiting list for liver transplantation and was found to be an independent predictor of waiting list mortality (80). In patients undergoing liver transplantation, muscle mass has been shown to predict ITU stay, days of intubation, length of stay and survival (81).

There is a high incidence of malnutrition in patients admitted to critical care, Giner et al identified 43% of subjects were malnourished with significantly increased rates of complications ($p<0.01$) and mortality ($p<0.05$) (82). Accumulated energy deficit during ITU stay has also been shown to correlate with an increased risk of infective complications (83). Meta-analysis of intervention studies undertaken in ITU has demonstrated a mortality benefit of PN compared to delayed EN, suggesting the benefits of nutritional support and the hazards of not treating malnutrition (84).

Malnutrition appears to be associated with increased morbidity in patients undergoing abdominal surgery. However, it is difficult to assess the *independent* effects, since more severe underlying disease is usually associated with both declining nutritional status and increased complications. All of the above studies have identified malnutrition as a risk factor, often one of many, but there is no evidence of a direct causal relationship.

An alternative approach to establishing the presence of a potential relationship between malnutrition and poor clinical outcome is to examine the benefits of nutritional interventional studies. However, randomised controlled trials to assess the effects of nutritional intervention are extremely challenging to perform in acutely unwell post-operative patients. They are also limited by ethical constraints, since patients must eat or be fed in order to survive. Therefore intervention trials are often a comparison of two different feeding regimens, which in small

studies is often difficult to establish a significant effect, given the complexity of other medical interventions and patient variability (85).

Preoperative intervention in patients undergoing planned abdominal surgery has been shown to be effective. In a study of 1085 consecutive patients undergoing elective surgery Jie et al identified that 512 patients were at nutritional risk (86). At risk patients were subsequently treated with a minimum of 7 days of enteral or parenteral nutrition. Of the 120 patients with a high risk of malnutrition the complication rate was significantly lower in the pre-operative feeding group compared to control 25.6% versus 50.6% ($p=0.008$).

Early enteral nutrition in patients undergoing curative resection for malignant upper GI cancer was shown to reduce surgical site infections ($p=0.017$), chest infections ($p=0.036$) and anastomotic leaks ($p=0.05$), it also reduced length of stay compared to control management (87). In a study comparing post-operative PN to intravenous glucose administration Sandstrom et al demonstrated significant reductions in mortality and morbidity ($p<0.05$) in the PN group (88). Despite the methodological limitations and changes in clinical practice in more recent times this randomised interventional study does demonstrate the benefits of balanced intravenous nutrition on clinical outcomes.

Whilst there is a widely documented association between poor outcome and malnutrition with supporting evidence of the benefits of nutritional intervention, due to the nature of the association it is unlikely that studies will ever definitively show a direct causal relationship. Despite the limitations in the available evidence base there are sufficient data combined with clinical reasoning to consider that the two are strongly linked. This has resulted in the publication of numerous national and international guidelines that recommend nutritional assessment and appropriate interventions in all patients admitted to hospital (8, 89, 90).

2.3.3.3 Nutrition support

Nutritional intake is important to health and disease resistance. Providing adequate nutrition and hydration is usually considered a component of basic clinical care. This places certain ethical restrictions on clinical studies by potentially diminishing the magnitude of benefit derived nutritional interventions but nonetheless there is wide ranging evidence of the benefits of nutrition support across many settings, including perioperative nutrition (59).

Decisions regarding perioperative nutrition can be difficult and require careful consideration by an experienced multidisciplinary team(8). A judgement is made based on patient factors, likely clinical course and available evidence and guidelines. In broad terms patient factors that are taken into account include; nutritional status pre-operatively such as body mass index (BMI),

history of recent weight loss, recent oral intake and likelihood of resuming normal oral intake. These are the principles of the screening tools such as MUST (91). Identification of at risk patients should prompt a more comprehensive assessment by those with nutritional expertise and should also include history of specific nutrient losses, unusually high requirements or organ dysfunction.

2.3.3.3.1 Timing of nutritional support

The majority of patients undergoing GI surgery recover gut function quickly enough to resume normal diet before reaching a threshold for artificial nutrition. Therefore, treating everyone presumptively might not only cause significant morbidity but place considerable burden on health care resources and patients alike. Currently there are no clinical tools which help predict which patients will develop post-operative IF. Determining the optimum time to intervene with artificial nutrition has not been established, often requires complex decision making, lacks a definitive evidence base and is likely to vary significantly between individual patients. Despite these challenges there are studies which help form the basis of current clinical practice.

A number of historical studies attempted to evaluate the potential benefits of routine pre-operative PN in patients undergoing surgery. In a study of 100 patients at high risk of post-operative complications Bellantone et al demonstrated that elective pre-operative PN did not reduce the mortality or length of stay (92). In subgroup analysis those who were defined as malnourished (based on serum albumin and/or total lymphocyte count) did have a reduction in septic complications. Other authors have also investigated the potential benefits of routine pre and post-operative PN in major complications in GI surgical patients, although the benefit was also only seen in those patients who were severely malnourished (93, 94).

Studies in healthy volunteers have shown significant reductions in muscle function and physical work capacity following 5 day fasts (95, 96). Detrimental effects on other systems after prolonged fasts are also reported (59). Data from these limited studies and expert opinion have led to similar recommendations from NICE and ESPEN suggesting that PN should be commenced in patients with a non-functioning GI tract and have consumed little or nothing for 5-7 days (8, 97).

In a study of over 1000 patients undergoing intestinal surgery Neumayer et al assessed the impact of post-operative nutrition support on length of stay and hospital costs (98). After controlling for severity of illness, those who received early feeding (within 48 hours either enteral or parenteral) at a minimum of 60% of their estimated requirements had a significantly reduced length of stay (11.9 days) compared to those who were fed early but insufficient (13.3 days), sufficient but late (14.6 days) or neither early nor sufficient (14.8 days). They also had lower health care costs.

In a recent large multicentre randomised control trial of over 4600 patients at nutritional risk Casaer et al investigated the effect of initiating PN either early or late to supplement insufficient enteral nutrition (99). Patients received the maximum tolerated enteral nutrition and were then randomised to receive additional PN to meet estimated requirements either on day 3 or day 8. There were significant benefits seen in the delayed group including earlier discharge from ITU (P=0.04), earlier hospital discharge (P=0.04) and reduced infections in ITU (P=0.008). However the majority of patients in this study had undergone non-GI surgery and therefore were more likely to having functioning alimentary tracts, allowing some enteral nutrition. At day 7 in the 'delayed' PN group the median total energy intake (EN/oral) was nearly 50% of predicted total requirements.

This study demonstrated significant differences between the two groups which the authors attribute directly to the late initiation of PN treatment. Another explanation of these findings is that the benefits in outcome were seen in those critically unwell patients who had a gradual increase in total energy input over a period of days by whichever route, supplemented with PN after 1 week if requirements were still not met. The logic for this alternative explanation centres around altered metabolic handling and demands during the early phases of critical illness and is discussed in section 2.3.3.3.2 (85).

Many of the studies regarding perioperative nutrition are over 20 years old, in that time there has been significant changes in clinical practice with the widespread adoption of laparoscopic techniques and enhanced recovery after surgery programmes (26). In addition there have also been changes with regard to PN indications and concerns regarding excessive levels of feeding which perhaps make these historical studies difficult to interpret and apply in the context of current clinical practice.

In reality a whole host of factors contribute to the decision to start post-operative PN. This not only includes patient factors such as the complexity of surgery and clinical progress in the first few days post-operatively, but also the relative availability of PN and expertise on different days of the week (15). Unless more definitive studies are performed, which seems unlikely given the complexity and both financial and ethical constraints it is unlikely that current guidelines are going to change significantly in the future.

2.3.3.3.2 Energy and nitrogen requirements in intestinal failure

Contrary to thinking in the not too distant past, data from studies using indirect calorimetry now support the view that most patients with critical illness do not have markedly raised energy requirements (100, 101). In a group of 50 acutely ill surgical patients Mann et al demonstrated predictive equations (Harris-Benedict) over estimated energy expenditure by an average of 59%

compared to measured energy expenditure (102). Zauner et al identified average resting energy expenditure of critically ill patients to be 23kcal/kg/day, irrespective of the presence of sepsis. Indicating patients who are inactive yet moderately stressed have resting energy expenditure close to baseline (103). These data and studies from others have led ESPEN to recommend a more modest figure of approximately 25 kcal/kg as estimated daily energy expenditure (97, 104, 105). Furthermore, with acceptance that hyperalimentation actually adversely affects clinical outcome and that recommendations regarding energy requirements for acutely ill patients are not significantly elevated from baseline, there has been increasing interest in the potential benefits of hypocaloric feeding, in the initial stages on nutrition support.

In a retrospective study of 183 patients in intensive care who had not undergone surgery, Krishnan et al undertook a study to compare clinical outcomes to recorded energy intake (106). After accounting for gastric aspirates, severity of illness, nutritional status and route of feeding, patients with moderate intakes (9 to 18 kcal/kg/day) were significantly more likely to achieve spontaneous ventilation before ITU discharge and were more likely to survive although this did not reach statistical significance. Compared to low levels of feeding (<9kcal/kg), higher levels (19-25kcal/kg) were associated with significantly lower likelihood of both hospital discharge alive and spontaneous ventilation before ITU discharge. Further sub-group analysis of the sickest patients showed that survival was significantly better in the group who received the lowest levels of feeding <9kcal/kg.

These findings are consistent with other studies assessing the optimal timing for PN administration and/or energy requirements. In a randomised controlled trial of 240 patients Arabi et al compared permissive underfeeding of 60-70% versus targeted feeding of 90-100% of predicted energy requirements, yet controlled for nitrogen intake (107). Despite attempts at targeted EN feeding there was only a relatively small difference between the two groups in terms of calorie intake, 59.0 % +/-16.1% versus 71.4 +/-22.8% in the targeted group, although this did meet numerical significance (<0.0001). There was no significant difference in 28 day all-cause mortality but there was a significant reduction in hospital mortality in the underfed group, RR:0.71;95% CI: 0.50, 0.99; P=0.04. It seems unlikely that such a modest difference in feeding rates would have a meaningful clinical effect but does highlight that the outcomes in both groups were largely similar and the difficulty of achieving target energy requirements, even in clinical trials.

It is generally agreed that early attempts at EN are beneficial in critical care but it is frequently noted that patients fail to reach target levels within the first 2-3 days of ITU admission (108). A number of recent studies have examined the potential to optimise energy intake with PN from

days 3-8 (99, 109). Casaer et al identified those with delayed PN use (day 8) were significantly more likely to survive ITU with a shorter length of stay, lending weight to hypocaloric feeding in the early stages of critical illness.

Serious illness and trauma result in a significant catabolic response, consisting of both an increase protein breakdown from the muscle reservoir and protein synthesis at sites of tissue injury and for generation of acute phase proteins. Consequently there are huge nitrogen loses that cannot be reversed despite any level of nutrition support. Current guidelines and expert opinion suggest providing 1.2-1.5 g/kg/day of protein in critical illness in most situations (97, 110, 111).

Hoffer et al suggest higher levels of protein 2.0-2.5g/kg/day may be beneficial in critically ill patients, improving nitrogen balance and permitting small but important increases in protein synthesis(112). However even in his own systematic review on which these recommendations are based it was noted that many of the studies were underpowered, poorly designed, had unclear definitions and were heterogeneous. Hoffer et al utilised data from the recent EpANIC study and extrapolated protein intakes between the early and late groups (99). Estimates that the delayed PN group had protein intakes of approximately 0.1g/kg for the 15 day observation compared to the early PN group the early group of approximately 0.7g/kg. Although not specifically designed as a 'low versus high protein intake' study the outcomes were better in the delayed PN group, which may relate to the very low protein provision.

One possible explanation as to why low levels of protein provision may be beneficial relates to differences in substrate requirements in catabolism. Reeds et al have demonstrated that acute phase proteins have a relatively higher content of phenylalanine, tryptophan and tyrosine compared to transport proteins or muscle (113). Therefore in critical illness, provision of amino acids in relative concentrations required during normal homeostasis will provide some substrate for production of acute phase protein synthesis but also a relative excess of amino acids which are not required during critical illness. This excess of immediately unwanted amino acids requires metabolising, diverting processes into non-essential tasks presumably with other metabolic consequences.

Much of these data regarding optimal timing, energy and protein requirements is heterogeneous and difficult to draw clear conclusions from, which is reflected in the variation between guidelines from clinical societies. Considerable amounts of the data relate to patients with critical illness and therefore is of some relevance in acute IF, however approximately 50% of all patients given PN in the UK receive it in non-critical care beds and therefore it seems likely that their metabolic stress and therefore nutritional requirements differ to some extent from those with more severe physiological demands (15).

Nutrition support is only a relatively small component of the multifaceted treatments and interventions occurring in critical illness, therefore it is easy to understand why it is difficult to demonstrate significant changes in clinical outcomes following relatively modest adjustments to feeding regimens. JeeJeebhoy noted some years ago that 'the benefits of nutritional support are evident when too little nutrition is given for too short a time to have any noticeable influence on lean body mass or circulating protein' (63). Whilst there are still large gaps in the evidence base in acute illness it seems reasonable to take a cautious approach in the early stages of PN support.

Following the immediate critical period and subsequent clinical improvement, modest levels of feeding should be increased to 25-35 kcal/kg/day, with a protein constituent of 0.8-1.5g/kg/day in accordance with national guidance (8). Data from a UK wide audit demonstrate that the median duration of PN treatment was 8 days, with 93.02% of patients requiring less than 30 days (15). These data suggest that most patients do not require long periods of treatment and therefore individual optimisation of energy and protein requirements seems unlikely to make significant differences to clinical outcomes given numerous other variables.

In contrast, those patients identified at an early stage as having type 2 or type 3 IF it would seem logical to optimise energy and protein intakes and preserve body composition and function. However this needs to be balanced against the overprovision of nutrients at times of metabolic stress and potential for long-term harm.

In the early days and weeks most patients with type 2 IF will be dependent on PN, but many manage some enteral intake and in the medium term it may be possible to wean off intravenous nutrition entirely. In their series of patients with ECF, Datta et al reported 36% (20/55) of patients were receiving PN at the time of referral, following optimisation at a specialist centre only 12/55 required this in the medium term, the remainder being managed with a combination of oral and enteral nutrition (34).

Lipids are an important constituent of parenteral nutrition, both as a source of non-protein energy and essential fatty acids. There is good evidence to suggest that the lipid dose should be less than 1g/kg/day in the majority of type 3 IF patients, to help reduce the development of intestinal failure associated liver disease (IFALD) (114). Lipid emulsions containing a mixture of long-chain and medium-chain triacylglycerol, high monounsaturated fatty acids and fish oil emulsions may reduce cholestatic liver complications compared to soybean based emulsions and are often used in preference (115, 116). There are no recommendations for type 2 IF patients, indeed it may even be harmful in those acutely unwell to restrict the lipid content. However in patients whom it is apparent will require long-term HPN a reduction in the lipid dose should be considered at an early stage.

Carbohydrates are the main energy source in PN formulations. In patients with critical illness there are high levels of insulin resistance, therefore provision of PN in this setting can further exacerbate hyperglycaemia. Hyperglycaemia is associated with increased morbidity and mortality in critical care settings. Van den Berghe et al demonstrated that intensive insulin therapy to maintain normoglycaemia (blood glucose 4.5-6.1 mmol/L) compared to conventional treatment was shown to reduce mortality in those patients requiring intensive care treatment for more than 3 days (52.5% versus 43.0% p=0.009) (117). There was no reduction in mortality when intensive care stay was less than 3 days (37.3% versus 40.0% p=0.33). However, there were reductions in kidney injury, ventilator weaning and intensive care length of stay.

In a subsequent larger study Finfer et al undertook a randomised controlled trial in 6104 patients who were assigned to intensive insulin therapy (target blood glucose 4.5-6.0mmol/L) compared to conventional control (10.0 mmol/L or less) (118). The 90 day mortality rates were 27.5% in the intensive insulin therapy group compared to 24.9% in the control group (odds ratio, 1.14; confidence interval 1.02 to 1.28; P=0.02). Hypoglycaemia was identified in 6.8% of intensive insulin therapy patients compared to 0.5% of control patients (P<0.001).

On the basis of these trials and other studies current guidelines have not made recommendations regarding glucose control, other than avoiding hyperglycaemia (119). It must also be noted that these studies were performed in patients in critical care settings, where high nurse to patient ratios allow intensive monitoring and changes in insulin regimens which are not practical on general wards. If intensive insulin regimens were adopted on general wards it may result in a significant increase in hypoglycaemia events.

2.3.3.3.3 Fluid and electrolyte needs in acute intestinal failure

Patients with acute IF often have unusual losses of fluids and electrolytes which require careful assessment and replacement. Fluid and electrolytes issues usually begin in the perioperative stage before the onset of intestinal failure. During major abdominal surgery large volumes of intravenous fluid are often required to maintain cardiac output and organ perfusion. This is important in acute IF as many patients will have had more than one operation and received significant volumes of intravenous fluid.

The stress response to surgery results in an anti-diuresis mediated through the renin angiotensin aldosterone axis, catecholamines and vasopressin, therefore sodium and water are retained. In patients who are catabolic there is a reduction in the ability to concentrate urine as a result of increased solute load, consequently sodium and chloride excretion are diminished. Therefore the provision of an excess of intravenous fluid results in retention of sodium, chloride and water

resulting in interstitial oedema, pulmonary oedema and in rare cases death. Alternatively, inadequate intravenous fluid replacement results in reduced organ perfusion, tissue hypoxia and progressive organ dysfunction.

In a meta-analysis of over 800 patients undergoing elective open abdominal surgery Varadhan et al reported those who were in fluid 'balance' had significantly fewer complications (RR 0.59 (95% CI 0.44, 0.81), P=0.008) and shorter length of stay (weighted mean difference -3.44 (95% CI -6.33, -0.54)d, P=0.02) than those who had fluid 'imbalance' (120).

The fluid balance of patients in critical care is closely monitored and adjusted by intensivists, often with the use of specialist monitoring not available outside of this setting. Approximately 50% of PN is administered outside this environment where fluid balance is scrutinised less intensely. The NCEPOD report highlighted concerns regarding fluid prescribing, reporting 28.3% of patients were being prescribed an inappropriate volume of intravenous fluids and 18.9% of patients were being prescribed an inappropriate type (15). The inference in the report is one of excessive or careless prescription of intravenous fluids.

Brandstrup et al undertook a study to assess the effects of intraoperative and postoperative intravenous fluid restriction in a multicentre observer blinded randomised controlled trial of 172 patients undergoing elective colorectal surgery (121). The restrictive regimen aimed to maintain preoperative body weight, the standard regimen resembled everyday practice. On the day of surgery the restricted regimen received a median of 2740 ml (range 1100ml to 8050ml) compared to 5388 ml (2700ml-11083ml) in the standard group. The restricted group also received less on the first day postoperatively. The restricted group had significantly reduced postoperative complications (33% versus 51%, P=0.013). The number of cardiopulmonary and tissue healing complications were also reduced. There were also 4 fewer deaths although this was non-significant. Similar improvements in outcome measures were identified in a smaller UK based study (122).

Not all studies assessing fluid restriction have demonstrated similar outcomes. In a study of postoperative fluid restriction in patients undergoing elective abdominal surgery Vermeulen et al stopped their study due to significantly increased risks of major complications in the restricted group, 40% versus 16% (absolute risk 0.24(p5% CI:0.03-0.46)). Similar lack of benefit was reported by Boland et al in their meta-analysis (123). This heterogeneity in the literature is likely to reflect differences in patient cohorts, study designs and degrees of fluid restriction, resulting in those studies with lower fluid provision giving too little and resulting in adverse outcomes. Despite these discrepancies adjusted perioperative fluid regimens are becoming widely adopted in clinical practice, either as restricted or goal directed regimens (26).

Assessing losses of nasogastric aspirate, stoma output and urine output in relation to hydration status, oedema, renal function and electrolyte balance is a fundamental part of the nutritional considerations in all IF patients who receive PN. However in those with more severe acute IF these can be very abnormal and be prolonged over many weeks. They therefore require special consideration.

As mentioned previously many patients develop type 2 IF as a consequence of ECF. These fistulae can occur in a proximal part of the small bowel and result in high volume losses, commonly over 2000 millilitres of fluid per day which contains very high electrolyte contents. Similarly, in patients with uncontrolled abdominal sepsis or mesenteric infarction a very proximal jejunal stoma is created to divert enteric contents, these again are frequently high volume in nature. It is therefore important the volumes from different stomas and fistulae are recorded accurately to help guide replacement.

Many IF patients referred to specialist centres have complex enterocutaneous fistulae involving bowel, stomach, pancreas, biliary tree or bladder. These fluids have high concentrations of sodium, potassium, bicarbonate and other electrolytes (table 2.5) (124). High volumes and/or sustained losses of these fluids not only cause significant abnormalities when measured on routine laboratory biochemistry but can also result in total body electrolyte deficiencies. In some patients, particularly those with short bowel syndrome, these outputs and losses can be exacerbated further by increasing oral food and fluid intake.

Table 2.5 Electrolyte contents of abdominal fluids

Fluid	**Sodium (mmol/L)**	**Potassium (mmol/L)**	**Chloride (mmol/L)**	**Bicarbonate (mmol/L)**
Gastric fluid	20-60	14	140	-
Biliary drainage	145	5	105	30
Pancreatic drainage	125-138	8	56	85
Jejunal	140	5	135	8
Ileal	100-140	5	75-125	0-30
Diarrhoea	30-140	30-70	-	20-80

It has been established that nearly 90% of prescriptions for intravenous fluids are written by inexperienced junior doctors with 17% of patients developing an associated morbidity (125, 126). In patients with more complex fluid balance, such as those with acute IF, it would be expected that a higher level of errors are made. Therefore one of the key roles of the nutrition team prescribing PN is to consider fluid balance and communicate decisions with the clinical team. Furthermore it is important that in specialist centres there is sufficient expertise and flexibility to manage this complex cohort of patients on a daily basis.

Therefore assessing fluid losses not only involves knowledge of the type of fluid, volume of fluid loss, surgical anatomy and consequence of enteral intake but also an understanding of the normal physiological volumes and constituents of various bodily fluids. Based on this assessment it is possible to replenish for these losses by increasing or reducing the electrolyte content of PN. However there are often limits on these additions due to the potential to make the PN unstable and unsafe to infuse. In this situation additional intravenous infusions containing electrolytes are required. In patients who are metabolically unstable and require significant daily changes to PN regimens this requires expertise from a highly specialist pharmacist and usually requires on site aseptic compounding facilities.

2.3.3.3.4 Routes of nutrition support in intestinal failure

The main aim of nutritional intervention in acute IF is to enable patients to resume oral diet or enteral nutrition as soon as it is safe and effective to do so. In patients who have undergone

abdominal surgery the clinical picture can change significantly within a matter of hours with corresponding changes seen in GI function.

The routes through which nutritional intake is maintained varies between patients across the course of their illness. Datta et al reported that the majority of patients had passed the acute septic phase at the point of transfer to their unit, with 20 of 55 patients receiving PN at that stage, a further 12 patients required it during the initial period of treatment and stabilisation within their unit (34).

During the initial acute septic phase oral or enteral nutrition may actually be detrimental if intestinal fistulae drain into blind ending abscess cavities, promoting sepsis. It may also be detrimental in patients with short bowel and very proximal stomas resulting in high outputs. As the clinical situation stabilises, the abdominal anatomy is clarified, sepsis is controlled and gastrointestinal function improves, alternative routes of nutrition can be explored.

Short bowel syndrome is a common clinical problem in acute IF. It is characterised by a reduction in the absorptive mucosal surface area and typically results in increased intestinal losses of fluids and electrolytes, restrictions in enteral nutrition to limit intestinal losses and accelerated intestinal transit time. Similar effects can occur as a result of enterocutaneous fistulae diverting intestinal contents, creating a 'bypass' of large areas of luminal surface. The clinical manifestations and severity of SBS are dependent on the remaining bowel length in continuity, anatomy, function and adaptive potential.

SBS results in problems with protein-energy malnutrition, sodium and water depletion, hypomagnesemia and vitamin and trace element deficiencies particularly B12, selenium and fat soluble vitamins. The management of SBS focuses on strict restriction of oral fluids volumes, in particular limiting hypotonic fluids and or substitution with controlled volumes of a glucose-saline 'electrolyte mix' solution. Treatment with antimotility drugs, antisecretory drugs and correction of hypomagnesemia is often required (127). It requires intensive input from specialist dieticians to manage this treatment and modify dietary intake. The success and duration of treatment are dependent on numerous factors but many patients are able to be weaned off intravenous therapy and managed solely on modified oral intake. Some patients require lifelong treatment even after restorative surgery.

In their study Datta et al identified that 38 of 55 patients required nasoenteric tube feeding and 37 patients were given oral nutritional supplements at some stage of treatment (34). Following a standardised but flexible approach to providing nutrition support in their cohort 33 patients were able to receive more than 50% of their requirements as normal food. This reduction in PN is

likely to have had considerable physical benefits and important improvements in psychological health, particularly for those patients who for clinical reasons had to wait a considerable time to undergo definitive reconstructive surgery.

In some patients with an ECF it may be possible to insert a gastrostomy feeding tube into the intestine distal to the fistulae through which the patient can be feed (fistuloclysis). It may be possible to provide all nutritional requirements using this method or at least reduce PN requirements. In a study of selected PN dependent patients with jejunocutaneous or ileocutaneous fistulae with mucocutaneous continuity Teubner et al treated 12 patients with fistuloclysis, reporting the successful withdrawal of intravenous nutrition in 11 patients. Only one patient restarted PN and there were no reported complications (128). In selected patients this techniques offers a great many advantages and obviates the potential risks from central venous access.

2.3.3.4 Complications of parenteral nutrition

Complications of PN treatment are common, catheter complications are reported to occur in 26% of patients and metabolic complications in up to 40%, although these figures depend on the definitions adopted (15).

2.3.3.4.1 Infective complications

Infective complications of parenteral nutrition usually relate to CRS or catheter exit site infections. Much of the data assessing causes and risk factors for CRS have focused on their use in a general setting, often in critical care, rather than solely in the context of hospital PN. However the majority of these data are probably generalizable to PN patients. The paucity of data in PN patients likely reflects the fact that most institutions will not treat sufficient numbers of patients to run formal trials or report outcome measures.

Catheter related blood stream infection (CRBSI) is a clinical definition that requires microbiological testing that specifically identifies the catheter as the source of infection (129) . In clinical practice it is often difficult to establish a diagnosis of CRBSI due to variations in practice such as; appropriate blood cultures not being taken, central catheters not being removed, differences in microbiological testing techniques employed or variations in individual clinical practice and adherence to guidelines. Alternative terminology has been developed to denote the presence of CRS where lesser degrees of microbiological proof are available, catheter-associated blood stream infection (CABSI) and catheter-suspected blood stream infection (CSBSI)(129). In this institution these definitions were adapted with a consultant microbiologist in accordance with available testing facilities to develop a local classification (table 2.6).

Table 2.6 Classification of catheter related sepsis

Type of infection	**Definition**
CRBSI	Patient must have both: 1. Laboratory confirmed peripheral blood stream infection: • With CVC in-situ • Within 48hrs of removal 2. Laboratory confirmed evidence of CVC colonisation • >10 CFU† of same organism from catheter tip culture • Same organism isolated from blood culture* taken via CVC where DTP‡ is ≥2hrs CVC:peripheral • Same organism isolated from exit site
CABSI	Patient must have both: 1. Laboratory confirmed peripheral blood stream infection • With CVC in-situ • Within 48hrs of removal 2. Clinical syndrome compatible with CVC infection with no clinical evidence to support infection at another site
CSBSI	Patient must have all 5 of: • Negative blood cultures • Treatment with antibiotics active against likely pathogens • Clinical syndrome compatible with CVC infection • Clinical improvement on removal of CVC or appropriate treatment • No other source of infection likely

Laboratory-confirmed bloodstream infection: patient must have either:

1. 1 or more recognised pathogens cultured from 1 or more blood cultures
2. Both:
    - A common skin organism cultures from 2 or more blood cultures drawn on 2 separate occasions or 1 occasion prior to appropriate antibiotics
    - Clinical sepsis: fever>38^{o}C, chills or hypotension

† colony forming units

* simultaneous peripheral and central blood cultures of same 10ml volume where initial 10ml of central sample has been discarded

‡ differential time to positivity

(Adapted from Bion et al (129))

In the UK 78% of PN is administered via a central rather than peripheral vein, the majority of which is administered as a short term treatment and therefore most venous access devices are non-tunnelled (15). Data from the NCEPOD report indicate that approximately 13% of catheters used for PN had a confirmed or suspected infection (15). Rates of CRS from UK centres vary from 0.7 to 6.7 episodes per 1000 catheter days (130, 131). Although data from both these observational studies were published in the context of nutrition team interventions from specialist IF centres, therefore may not be representative of UK practice as a whole.

There are four potential routes of contamination in central catheters; migration of skin microorganisms at the insertion site, direct contamination of the hub, haematogenous spread from a distal site of infection and rarely infusate contamination. An American nationwide prospective surveillance study of nosocomial blood stream infections in 49 hospitals over a 7 year period identified 24179 infections. Central venous catheters were in situ in 17484 (72%) of patients, 5791 (24%) of patients were receiving PN (132). The infectious organisms identified were coagulase negative staphylococcus accounting for 31% of isolates, staphylococcus aureus 20%, enterococci 9% and candida species 9%.

There are a large number of variables that influence the rate of CRS, these are wide ranging and are beyond the scope of this review. Detailed national guidelines based on the large volume of published literature provide evidence for best clinical practice (133, 134). Much of the evidence base and recommendations rightly focus on technical aspects regarding central venous catheters such as catheter type, catheter site, sterile barrier precautions during insertion, skin preparation, catheter care and quality improvement interventions. Many of these individual recommendations and interventions could be achieved through standardisation of protocols and equipment.

In a prospective multicentre study of a bundled intervention consisting of 5 evidence based aspects of clinical practice in intensive care, Pronovost et al reported a significant reduction in the median rate of CRS from 2.7 infections per 1000 catheter days to 0 at 3 months ($P<0.002$) in a period that consisted of over 375,000 catheter days (135). These results were sustained at 18 months of follow-up. In addition to basic technical modifications to clinical practice this study engineered changes with regard to the ethos of CRS. They did this through a range of indirect measures such as taking owner ship of the problem and addressing it specifically by means such as designating individuals as team leaders to assist in education and reporting. Despite a number of limitations in the study design it does demonstrate that wholesale adoption of inexpensive patient safety measures appear to have profound effects on morbidity and healthcare costs.

There have been other observational studies reporting improvements rates of CRS following the introduction of NST. Hvas et al report a reduction in CRS from 6.7 to 0.7 episodes per 1000 catheter days (P<0.001) following the introduction of a NST to clinical areas outside of the intensive care unit and IF unit (130). Similarly Kennedy et al reported a 29% reduction in CRBSI following the introduction of NST (131). Despite the observational nature of these studies it does appear there is an association between patient safety interventions and reductions in CRS complicating PN use in hospitalised patients.

Despite numerous trials and interventional studies aiming to reduce the incidence of CRS through different insertion techniques, catheter types and catheter access techniques very little is known about CRS in PN patients in non-critical care beds. Several authors have reported low rates of CRS in intestinal failure units and following the introduction of NST (33). However, there are no published data on the effects of establishing an intestinal failure unit on rates of CRS within an institution.

2.3.3.4.2 Catheter occlusions

Catheter obstruction is most commonly due to intraluminal precipitation of drugs including PN, mechanical problems or thrombosis. Occlusions can be partial or complete and are thought to affect up to 25% of CVCs that are placed (136). CVC occlusion can delay treatment, increase the risk of endoluminal bacterial adhesion and subject the patient to the need for catheter replacement. PN precipitation can be prevented by using appropriate catheter care protocols and use of infusion pumps (137). Mechanical occlusion occurs most commonly from catheter malposition. Thrombotic occlusions occur in two distinct forms, a failure to flush the catheter correctly can result in intraluminal clot formation. Secondly, shortly after the catheter is inserted a fibrin build-up starts to occur on the surface. The fibrin can be deposited inside the CVC, around the wall of the blood vessel or as a fibrin sheath as a layer on the outside of the catheter.

There are a number of techniques that have been employed to unblock occluded catheters. These have focused on the likely cause of the occlusion and using the following substances; ethanol for lipid, hydrochloric acid for drugs and urokinase or recombinant tissue plasminogen activator for clots (137). Although the number of studies undertaken in this area is small and the data of variable quality a recent Cochrane analysis revealed some evidence that demonstrated urokinase was more effective than placebo in restoring patency (RR 2.09, 95% confidence interval 1.47 to 2.95), with a number needed to treat of 4 (138).

In patients requiring long term catheters for HPN or in those with difficult vascular access there is a greater importance of re-establishing catheter patency in those presenting with occlusion. The

use of mechanical endoluminal brushes has been shown to be effective in achieving patency. In a recent study of over 134 catheter occlusions, Allan et al demonstrated a significant increase in the proportion of catheters where patency was established with the use of this technique, 86% versus 50% (P<0.0001) (139). Consequently there was a significant reduction in the number of catheters requiring replacement.

2.3.3.4.3 Venous thromboembolism

Central venous access devices are associated with deep vein thrombosis (DVT) and pulmonary embolism, increasing morbidity, mortality and cost. A recent meta-analysis reported PICC related DVTs were identified in 13.91% of patients who were critically ill (95% CI 7.68-20.14). Chopra et al identified 11 studies comparing PICCs to CVCs and demonstrated an increased risk of DVT in PICC patients (OR 2.55, 1.54-4.23, p<0.001) (140). However, only 1 of these 11 exclusively related to PN, which reported no increased difference in DVT rates (141). Also in this meta-analysis, 3 of the studies only included patients in critical care with significant variation in the rates of reported DVT 2.8 to 27.2% compared to triple lumen catheters where the incidence of thrombosis was just over 1% in most studies(142-144).

There are a number of potential explanations why PICCS appear to have a higher rate of DVT related complications which include; PICCs occupying a greater luminal area than CVCs, repeated movement of the arm resulting in intimal trauma and longer dwell times compared to CVCs. Despite the increased prevalence of DVTs in PICCs pulmonary embolism is infrequent.

Data from the 2010 NCEPOD study revealed poor practice regarding many aspects of CVC care, estimating complications occurred with 26% of CVCs. Only 67.4% of patients had catheter site documented in the notes, however when this was documented it was deemed appropriate in 95.1% of cases. There were other aspects of poor documentation that were noted in the study; the type of catheter was recorded in only 73%, tip position documentation 45.5%. Other relatively common complications included occlusion, misplacement, accidental removal, fracture and thrombosis

Catheter complications are thought to be a relatively frequent complication in type 2 IF, although there are no published data regarding the frequency. This type of complication is perhaps unsurprising given the often prolonged critical care stay and duration of PN treatment. Whilst interruption in treatment to due catheter occlusions and CRS are problematic in the short term it is crucial to avoid thrombosis in the central vasculature, particularly given that approximately 50% of patient will remain dependent on long-term HPN. Indeed central venous catheter thrombosis in 2 central veins is an indication for consideration of small bowel transplantation (145).

2.3.3.5 Metabolic complications of nutrition support

In the recent nationwide NCEPOD study metabolic complications were reported in 39.3% of patients receiving PN, with hypophosphataemia, hypokalaemia and hypomagnesaemia being the most frequently reported events. 49.4% of metabolic complications were potentially avoidable with 15.5% managed inappropriately even when recognised.

Many of the 'metabolic complications' recorded by audits such as the NCEPOD report are probably reflections of the difficulties in determining fluid and electrolyte requirements, which also are very changeable in acute IF, as discussed above. However, acute IF patients can often become malnourished before appropriate nutrition support is instigated and hence, as a group, they are also prone to metabolic complications from refeeding phenomena.

The term 'refeeding syndrome' lacks a consensus definition but has been used for many years to describe a broad range of metabolic consequences that can occur as a result of providing unbalanced nutrition to malnourished individuals. Early observations identified significant adverse cardiorespiratory and neurological complications as a consequence of starvation studies (146). Further studies and observations have influenced the literature resulting in the following description being incorporated into the NICE guidelines 'life-threatening acute micronutrient deficiencies, fluid and electrolyte imbalance, and disturbances of organ function and metabolic regulation that may result from over-rapid or unbalanced nutrition support' (8).

In order to maintain homeostasis, the cellular machinery of the body requires a constant supply of energy. An estimated two-thirds of resting energy expenditure is consumed through synthesis and degradation of macromolecules and the movement of material across membranes. When the energy demand is unmet by dietary intake the body is forced to utilise tissue reserves as an energy source, resulting in loss of weight and reductions in tissue function. The pathology of malnutrition occurs as an adaptive down regulation process, reducing metabolic activity and therefore reducing energy demands.

Efficiencies are achieved by reducing the amount of external physical activity and decreasing the activity of internal energy-consuming processes such as membrane pumping. The Na/K ATPase pump plays a significant role in maintaining the relative distribution of intracellular potassium and sodium. Down regulation of this pump results in intracellular and subsequent whole body potassium deficiency. It is accompanied by intracellular sodium accumulation along with movement of water into cells. There are also reductions in intracellular magnesium, phosphate and calcium.

The provision of nutrients rapidly reverses these energy dependent processes. Carbohydrate stimulates the release of insulin, which results in an increase in cellular uptake of phosphate, magnesium, potassium and glucose, causing a decrease in the serum concentration. The movement of sodium and water out of cells with up-regulation of the Na/K ATPase pump results in circulatory overload. Deficiencies of micronutrients, particularly thiamine compound these problems and are characterised by classical but thankfully rarely seen presentations of wet beriberi and Wernicke-Korsakoff syndrome.

Refeeding complications can be prevented by better identification of at risk patients, which requires applied knowledge at the point of assessment. Data from the NCEPOD study reported that only 45.9% of patients were considered to have met the criteria for having had an adequate assessment (15). In addition refeeding problems can be minimised by feeding at low levels in the initial stages. UK guidelines have suggested cautious introduction of nutrition, no more than 50% of requirements (8). In those at high risk, even lower initial rates of feeding should be used, 10 kcal/kg/day. Appropriate rates of feeding should always be accompanied by provision of electrolytes and micronutrients to reduce the risk of ensuing complications.

Abnormalities of liver function tests are commonly seen in patients with acute IF, elevated aspartate aminotransferase 27%, alkaline phosphatase 32% and bilirubin 31% after 4 weeks of PN (147). These abnormalities are typically mild and in the majority of cases the cause is unrelated to PN and more likely to be the result of sepsis, drugs, ischaemia or intrinsic liver disease.

There is, however, a growing literature base with regard to hepatic complications in patients with type 3IF receiving long term PN. Hepatobiliary complications have a reported incidence of between 19% and 75%, with an incidence of intestinal failure associated liver disease affecting 0-50% of patients and a reported mortality of up to 22% (114, 148-150). The aetiology of IFALD is thought to be multifactorial and relate to underlying liver disease, sepsis, small bowel bacterial overgrowth, small intestinal length <50cm, lack of enteral nutrition and excessive and or type of lipid provision (151). The variable incidence and multifactorial causality of IFALD is likely to reflect differences in the underlying study populations.

Whilst a significant proportion of patients with type 3IF occur as a result of progressive disease it is also recognised that approximately 50% of patients with type 2 IF will go on to develop type 3 IF (3). Given that many patients with type 2IF have prolonged periods of critical illness, sepsis and altered metabolic demands it raises the question as to whether these individuals who then progress and become type 3 patients will be at higher risk of IFALD. Therefore, it would seem prudent to minimise potential hepatic complications at an early stage where possible.

Cyclical rather than continuous PN results in significant reductions in bilirubin and reduced insulin levels (152). It is clinically easy to achieve and cost neutral. It is standard practice in many units and recommended in clinically stable patients from day 14 (8).

2.3.4 Anatomy

In patients with type 2IF, a detailed assessment of the intra-abdominal anatomy is important for two reasons. In the first few weeks and months it is likely to contribute to the development of the subsequent management plan. At a later stage it is vital to have as much information as possible prior to undertaking challenging reconstructive surgery.

This assessment usually requires a combination of imaging modalities, contrast studies (oral, enema and fistulography) are frequently combined with cross sectional imaging and endoscopy to gain as much information as possible. In this setting barium tends to be favoured because it has a greater radiographic opacity compared to water soluble contrast and has a lower tendency to dilute and therefore has a higher sensitivity in identifying fistulae (50). Assessment of other organs systems may require further specialist imaging such as cholangiography or intravenous urography.

An assessment of small bowel and colonic length has important long term prognostic value in determining nutritional independence and may aid initial management. A number of studies have been performed to establish the relationship between remaining intestine and nutritional requirements and have been summarised by Nightingale et al (table 2.7) (127). This information is helpful when planning treatment prior to definitive surgery for example potential for weaning from PN or potential for fistuloclysis. It is also helpful in guiding patient expectations in the medium and longer term. It also aids surgical decisions regarding potential resection.

Table 2.7 Length of remaining bowel and requirements for long term nutritional support

Jejunal length (cm)	**Jejunum-colon**	**Jejunostomy**
0-50	PN	PN
51-100	ONS	PN
101-150	None	ONS + Electrolyte mix
151-200	None	Electrolyte mix

Whilst small bowel length is important, the presence of some colon in continuity also contributes to nutritional status and can be vital in achieving independence through its effects on fluid resorption and increasing energy recovery. The colon improves sodium and water reabsorption through aldosterone-sensitive sodium channels, Nordgaard et al demonstrated the presence of some colon in continuity reduces intestinal losses by an average of 3.5 litres(153). Better sodium and water status will reduce chronically raised aldosterone levels through negative feedback, reducing urinary potassium losses. The increased potassium availability then permits accretion of lean body mass (154).

The colon also produces glucagon-like peptide 2, which is an intestinal trophic growth factor increasing the absorptive surface area of the small bowel (155). The peptide YY is also produced by the colon which amongst other functions acts as a “colonic brake” to slow gastric emptying and hence increase absorption (156). In the colon there is also direct energy recovery as a result of colonic bacteria fermenting undigested carbohydrates and medium chain fatty acids which are then easily absorbed.

During the anatomical assessment information is also be gathered regarding the quality of remaining bowel. In patients who have Crohn’s disease or mesenteric ischaemia it maybe the bowel is of insufficient quality, either through stricturing or active disease and a resection at the time of reconstructive surgery may be required. In addition the presence of active Crohn’s disease may affect decisions to anastomose and require medical therapy prior to surgery. Similarly on-going ischaemia or compromised blood supply is an important pre-operative finding as it will threaten any surgical anastomosis.

2.3.5 Plan

Planning treatment based on immediate needs and anticipating the likely clinical course is a fundamental component of clinical practice. In acute IF it requires coordinated input from many medical specialties and extended multidisciplinary teams often over prolonged periods of time, particularly in those with type 2 IF who may have ongoing needs and support in the community.

One of the major decisions in type 2 IF is determining an individual's long term nutritional outcome and what level of intervention is required to achieve that aim. Following the successful resolution of the acute phase the outcomes can largely be divided into a number of categories; 1) Reconstructive surgery undertaken to achieve nutritional autonomy either following an extended convalescence in the community or during current admission 2) Reconstructive surgery with the intent of increasing extent of nutritional independence or quality of life but not free from artificial nutrition 3) No reconstructive surgery required to achieve nutritional autonomy 4) No further intervention possible and requirement for long term artificial nutrition/HPN or operative risk outweighs the potential benefits.

Reports from a single UK centre suggest that an estimated 50% of patients referred to as type 2 IF will require long term HPN without the prospect of achieving nutritional autonomy (3). A proportion of patients may not require further surgical treatment. Datta et el reported that 35 of 55 patients underwent reconstructive surgery, 4 patients had spontaneous fistulae closure, 5 patients the risk of surgery was deemed greater than the benefits, 5 patients had metastatic disease and 3 patients were able to manage with low volume fistulae (34).

2.3.5.1 Multidisciplinary approach

NSTs have been in existence for a number of years, established to facilitate the provision of safe an effective nutrition. A number of studies have reported the value of NSTs in improving the quality and safety of PN support. Hvas et al demonstrated that after the introduction of an NST despite an increase in clinical activity the percentage of referrals where PN was not initiated increased from 5.3% to 10.1% ($P=0.03$) (130). There was a reduction in the use for PN due to inadequate oral intake 11% to 3% ($P<0.01$), indicating more appropriate use. Kennedy et al reported that NSTs were also cost effective, preventing expenditure on inappropriate PN use and reducing the costs incurred from CRS (131). As a consequence of this and other evidence, national UK guidelines recommend that all hospitals should have a NST (8). Despite this, a recent survey identified that only 60.2% of hospitals have an NST (8, 15).

Evidence from other medical specialities demonstrated that management by specialist multidisciplinary teams in dedicated units improves morbidity and mortality. In a study of over

800 patients admitted with an acute stroke Tamm et al showed patients managed in a specialist stoke unit had a reduction in mortality from 17.1% to 8.3% (adjusted OR 0.54; 95% CI 0.31-0.95) compared to standard care. There were also significant differences seen in those discharged independently without increases in length of stay (157). Similar data exists for coronary care units, neonatal units and upper GI surgical units (158-160).

Evidence for the benefits of sub-specialisation is common in the surgical literature. Studies assessing the influence of surgeon volume and unit volume confirm a greater degree of specialisation is associated with improved clinical outcomes. In a study of 1856 patients undergoing elective colorectal cancer surgery in 16 UK centres Oliphant et al identified those operated on by a specialist colorectal surgeon compared to a non-specialist had a lower post-operative mortality (4.5 versus 7.0%; P=0.032) and 5 year survival was also better 72.2 versus 65.6%; P=0.012) (161) .

In patients undergoing surgery for rectal cancer Morris et al examined the use of abdominoperineal excision. They identified higher volume specialist surgeons undertook fewer resections and when they did perform this more complex operation the median distance of the tumour from the dentate line was lower (162). This suggests that greater experience and skill set may result in a different approach to the same problem, a concept that is potentially very important in IF surgery.

Similar arguments could be made for patients with type 2 IF, given the estimated low incidence, complex clinical decisions and the diverse expertise required to manage patients it would seem logical that managing patients in specialist units would be an appropriate model. This theory formed the basis for the development of the original IFU described by Irving et al which has been replicated at a few specialist institutions (33).

One of the challenges is identifying which patients would benefit from management in a specialist unit, there are no nationally agreed guidelines and there is considerable variation between institutions regarding local expertise. One national IF centre has developed criteria based on their own experience recommending when a referral to a specialist centre should be considered (table 2.8) (3). However, it is unclear how widely accepted or utilised these criteria are. It seems logical that adoption of a validated or universally agreed set of criteria for referral of acute IF patients as part of a national strategy would improve patient outcomes and potentially reduce costs.

Table 2.8 Criteria for referring patients with type 2 intestinal failure to a specialist centre

- Persistence of intestinal failure beyond 6 weeks and complicated by venous access problems
- Multiple intestinal fistulae in a totally dehisced abdominal wound
- Total or near total small bowel enterectomy (<30 cm of residual small intestine)
- Recurrent venous access problems in patients needing sustained parenteral nutrition
- Persistent abdominal sepsis, not responding to radiological and surgical drainage
- Persistent nutritional or metabolic complications relating to high-output fistulae and stomas, and/or to prolonged intravenous feeding
- Any patient with a persisting intestinal fistula beyond the expertise of the referring Hospital

A recent article by Donaldson et al has reported the benefits of a continuous quality improvement project to improve length of stay and therefore time on the waiting list prior to admission (163). Through implementing a number of structured improvements and changes in multidisciplinary working, length of inpatient stay was reduced from 55.7 days to 44.0 days and a reduction in waiting list time from 65.7 days to 18.5 days.

2.3.5.2 Wound care

Wound management in hospitalised patients with type 1 IF is less of a significant issue due to the availability of expertise and the relatively transient nature of the patient cohort. However, it can be very challenging particularly in type 2 IF, usually in the context of a large laparostomy. It can become the issue which dominates patients' recovery and prolongs hospitalisation due to the practicalities and availability of expertise in the community.

The management of large abdominal wounds pose a number of challenges. Intestinal fluid is caustic to the skin and may contain corrosive enzymes. It is important the skin around fistulae and wounds is protected to avoid progressive inflammation and secondary infection. Patients often find these wounds distressing and painful, requiring specialist nursing or stoma therapists to control the fistulae output. Devices which leak significantly limit patient mobility and recovery.

There is significant controversy in the literature and in clinical practice regarding how laparostomy wounds are best managed. Negative pressure wound therapy (NPWT) aims to remove exudate and infected material away from the wound, facilitating nursing care and delayed primary wound closure, reducing the need for prosthetic replacement of the abdominal wall. Alternatives to this include wound management bags such Eakin and Bogatoa bags. However, a number of specialists remain concerned NPWT promotes fistulation in cases where negative pressure is applied to exposed bowel (164).

In a prospective observational study of 578 patients recruited from 105 UK hospitals Carlson et al examined outcome measures in patients with laparostomy wounds who received NPWT and those who did not following a laparotomy for sepsis and trauma (165). In this cohort they report an overall mortality rate of 28.2%. The rates of fistulation (RR =0.83, 95% CI: 0.44-1.58), death (RR 0.87, 95% CI 0.64-1.20) and intestinal failure (RR = 1.00, 95% CI: 0.64-1.57) were no more frequent in those who received NPWT. The rate of delayed primary closure was lower (RR = 0.74, 95% CI: 0.60-0.90, P=0.002) when NPWT was used. However there was significant heterogeneity of the patient populations and a lack of data on illness severity which potentially limits the ability to make firm conclusions.

This study provides a useful insight into UK practice regarding laparostomy wounds. The authors highlight the apparent difference in surgical practice compared to North America where laparostomies are predominantly used in trauma situations for 'damage control' (166). In this UK study, the commonest indication for laparostomy was the management of sepsis, with NPWT used in 61% of patients. Importantly it does not support concerns regarding the increased morbidity and mortality form this technique.

2.3.5.3 Metabolic and nutritional optimisation

For the majority of patients with type 1 IF once the acute problem has resolved restoration of nutritional status will occur by with resumption of oral intake. Monitoring in the community may be necessary in the minority where there are other factors such as a chronic disease process or significant comorbidities. Most patients with type 2 IF will by definition have had prolonged hospitalisation, septic complications, critical care requirements and nutritional complications. The inevitable catabolism results in significant loss of physical reserves, muscle mass and a critical care myopathy. During the ensuing recovery, nutritional requirements will vary according to activity factor, enteral tolerance and longer term plans for nutritional autonomy.

The aim of nutritional support is to provide the highest proportion of requirements as possible from diet supported by artificial nutrition where required. In addition to the physiological benefits or normal diet it also has a significant psychological effect. Restoration of body composition may take many months, it is particularly important that patients gain lean body mass and not just fat therefore monitoring by an experienced dietitian is important.

2.3.5.4 Community support for artificial nutrition

The amount of support required in the community depends on the anticipated clinical outcome. A proportion of patients who require further surgery yet need a period of time to recover physically and psychologically are often discharged home and need very close monitoring especially as they are often discharged on enteral tube feeding or HPN. This can sometimes seem daunting for patients and carers who may have to also manage various stomas, wounds and catheters. In the UK this is supported by HPN teams and commercial community healthcare companies liaising with IF teams.

2.3.5.5 Treatment of underlying disease

Investigation and treatment of the primary pathology is potentially important in reducing risk of recurrence in the setting of Crohn's disease or those patients who had previously undergone surgery for cancer. The same is true regarding optimisation of comorbidities, particularly in relatively elderly patients considered suitable for further surgery.

Crohn's disease is reported to be the cause of 21% of cases of type 2 IF (22). Treatment for Crohn's disease with steroids, immunomodulators or biologic agents can result in reductions in inflammation and closure of fistulating disease. However all three classes of drug are associated with impairment of different aspects of the immune response and therefore may limit the potential use or timing of treatment in the acute phase. However there is rational for considering treatment on a case by case basis, particularly as positive histological inflammatory margins at the site of an anastomosis are associated with increased risk of septic complications in patients undergoing surgery (167).

In patients with mesenteric vascular disease investigations should be undertaken to identify the cause. In those with arterial infarction evaluation of the patency of the remaining blood supply and consideration of intervention may be required. Investigation of potential embolic causes is also important. In patients with venoocclusive disease investigation of thrombophilia and anticoagulation may be required.

2.3.5.6 Reconstructive surgery

Reconstructive surgery in type 2 IF is required in approximately 60% of patients referred to specialist centres and should only be undertaken when the patient is recovered (6). The timing and aims of surgery will vary between patients but broadly speaking should be to improve quality of life by achieving a greater degree of nutritional autonomy and closure of any ECF.

In the absence of published outcome data for all types of surgery undertaken in type 2 IF patients, data relating to surgery for ECF will be reviewed here since that is the commonest reported cause of type 2 IF. In those undergoing reconstructive surgery the ECF recurrence rates are reported to be 13%-34.9% with postoperative mortality rates at 30-90 days varying between 2.9-8% (34, 35, 55, 168). The overall reported mortality in patients with ECF including those who did not require definitive surgery from 2 UK centres which manage type 2 varies from 7.3-10.8 % (34, 35).

2.3.5.6.1 Timing of reconstructive surgery

Surgeons have anecdotally suggested waiting until there is evidence of prolapse of the intestine at the site of abdominal wall fistulation, indicating a reduction in dense intraabdominal adhesions (25, 169). In a study of 203 undergoing surgery to repair ECF Lynch et al identified that recurrence of fistulae was associated with the time since the last operation. Patients undergoing repair between 2 and 12 weeks after their last surgery had an ECF recurrence rate of 28% (10 of 36 patients). This was higher than those patients whose operation was delayed longer than 12 weeks, recurrence rate 15% (17 of 114 patients, P= 0.088) and those with operations within 2 weeks of surgery, recurrence rate 20% (4 of 20, P 0.37) (55).

In the study by Lynch et al the median time to surgery was 6 months from last operation, a similar time period of 8 months was reported by Hollington et al although analysis of recurrence rate and timing of surgery was not reported (35). Brenner et al retrospectively reviewed 135 patients undergoing ECF repair (168). They identified that patients undergoing surgery more than 36 weeks from diagnosis had a significantly higher rate of recurrence compared to those less than 36 weeks (adjusted OR 5.4 (95% confidence interval 1.8-16.4)). When examining the cohort of patients with a longer interval they identified a higher proportion of patients on enteral intake (55% versus 26%, P=0.04), prolonged medical management and large slow healing wounds. This suggests that there may have been different patient characteristics than those who underwent early surgery.

Brenner et al did not report the incidence of laparostomy wounds, which in the Hollington study occurred in 32 patients (19.2%). Although no sub-group analysis was performed it is noted that 6 (18.8%) of the patients with a laparostomy died, compared to 10.8% overall mortality inferring a

higher degree of complexity, although the numbers are very small. Additionally Brenner et al did not attempt to categorise the fistulae as to whether they involved multiple loops of bowel or an abscess, both of which would have required more complex surgery potentially increasing the recurrence rate and also a likely longer delay prior to surgery.

2.3.5.6.2 Surgical technique

Surgical repair technique was a significant predictor of ECF recurrence. In their study of 203 patients Lynch et al identified patients with a wedge repair or oversewing had a recurrence rate of 32.7%, compared with 18.4% if the ECF was resected (P= 0.004) (55). Brenmer et al also reported an 11% recurrence following resection and hand sewn anastomosis compared to 22% with an oversew and 35% with resection and stapled anastomosis (168).

2.3.5.6.3 Abdominal wall closure

In a relatively small defect it may be possible to achieve a primary closure. For larger wounds other methods include the component separation technique which involves the separation of the superficial abdominal wall from the underlying fascia. Further length can then be gained by dividing the posterior rectus sheath from within, potentially gaining up to 14cm of length in the abdominal wall per side without risking a further defect or hernia formation (170).

Larger defects require insertion of prosthetic material to close the defect. Fistula wounds are inevitably heavily contaminated preventing the use of traditional non-absorbable meshes used for standard incisional hernia repairs. Novel biological meshes that have been processed to acellular, porous extracellular matrices have allowed a 1 stage approach to closure of the abdominal defect. Native cellular growth into the mesh matrix allows incorporation into the tissue which may enhance resistance to infection. In a recent study of 80 patients with a ventral incisional hernia Itani et al reported 72% of contaminated herniae were successfully repaired with Strattice ™ mesh (171).

2.3.5.7 Psychological support

There are no studies specifically studying long-term outcomes in patients with type 2 IF. However data have shown an ICU admission with critical illness can have long-term consequences both in terms of physical limitations and psychological health, including reduced quality of life measures. In a study of 109 patients who had survived acute respiratory distress syndrome Herridge et al reported that 5 years after discharge from ITU with there was a median 24% reduction in exercise capacity compared to predicted, with additional reductions in the physical component score on quality of life scoring systems (172). There was also a consolation of other physical and

psychological problems in both patients and carers. Therefore with such a high burden of long term morbidity in critical illness survivors it is particularly important to support the proportion of patients with type 2IF who require further reconstructive surgery in the short to medium term.

2.3.6 Quality indicators in acute intestinal failure

The NCEPOD report described multiple deficiencies in the way in which acute IF is managed and high rates of complications in many units. One potential route to improve clinical practice would be to identify important standards which all hospitals should meet. These need to be easily identifiable and enable the data to be collected without significant additional resource. This would allow institutions to compare themselves to those standards and national averages. In type 1 IF this may include;

1. Number of patients treated with PN
2. Incidence of CRS in all patients receiving PN
3. The number of patients receiving PN for more than 28 days without discussion with a regional IF centre

Assuming there were universally accepted definitions of what constitutes IF surgery, then publishing unit success and complication rates would ensure standards were being met. The following criteria have been proposed by the ASGBI in the context of IF surgery.

1. Unplanned return to theatre after surgery for type 2IF (Bleeding, anastomotic leakage, intra-abdominal abscess)
2. Recurrent fistulation rates
3. Success of discontinuation of artificial nutrition support (PN, Parenteral fluids and fistuloclysis) in patients receiving reconstructive surgery
4. Hospital and 30 day mortality
5. Unplanned intensive care and hospital readmission rates.

It may also be appropriate to include a standard on time from referral to transfer and length of stay in those units accepting regional referrals. If centres reported this level of detail it is likely that standards for these criteria could easily be identified over time. This would promote the development and dissemination of best practice and ensure universally high standards of care.

2.4 Existing intestinal failure infrastructure

Most institutions providing services for acute admissions will manage patients who require PN. Therefore it is appropriate that there should be a team of professionals with expertise in this area with an infrastructure to ensure its safe administration. This was a key recommendation made by NICE in 2006, yet in 2010 results from the NCEPOD study identified that only 60% of hospitals had a NST (8, 15). In most hospitals more than 90% of the activity will be managing patients with type 1 IF.

However, inevitability some clinical practice will involve managing patients with type 2 IF, either in the early stages of acute illness before referring to a specialist unit or the patient is managed entirely within that institution. The extent of type 2 IF management provided by a particular institution will vary between individual units. This will largely be driven by the clinical expertise available locally, relationships with specialist IF units and geographical considerations.

In recognition of the extensive resources and expertise required to manage significant numbers of patients with type 2 and type 3 IF, in 1998 the National Commissioning Group designated two national IF centres: St Mark's Hospital and Hope Hospital. At times the national IF centres became overloaded with subsequent development of waiting lists for admission, causing pressures on referring hospitals. As a result d*e facto* several other hospitals have provided such services (5). However, these alternative providers for both type 2 and 3 IF have evolved without planning and nationwide service provision has been inconsistent in some regions.

In recent years it has been proposed that a national network of centres should be established to ensure adequate access to services. There have been a number of proposals regarding the exact format but this essentially includes national or quaternary units, namely the national IF centres and those providing small bowel transplantation, tertiary regional units and secondary care (5). The establishment of a properly funded national network should enable sufficient infrastructure and reporting mechanisms to ensure that quaternary and tertiary centres are closely regulated with regard to delivery of care.

2.5 Treatment costs

The NHS uses a complex rule based system named Payment by Results (PbR) for paying Trusts. Payments are linked to hospital activity and are adjusted for case mix. It was designed to ensure fair and consistent funding levels rather than to set budgets. PbR is supported by Healthcare Resource Groups (HRG) a classification framework that represents standard groupings of similar treatments which use common levels of healthcare resource. HRG codes are effectively used as

units of currency and also allow comparison of activity between different institutions. There is some flexibility in HRG codes enabling 'unbundling' of high cost elements of care that can be reimbursed as additions to the baseline tariff.

Through a complex process HRG codes are developed and attached to medical conditions based on International Classification of Disease (ICD) codes, an internationally recognised classification of diseases and healthcare problems. HRG codes also take into account surgical operations and procedures through a separate classification system based on OCPS (Office of Population, Consensus and Surveys Classification of Surgical Operations and Procedures).

In the case of IF and HPN there are many ICD and OCPS codes which identify conditions, such as Crohn's disease, where IF may sometimes be present but equally may not be present. However, there is no specific code for IF. Therefore the ICD and OCPS cannot be used for identifying IF cases and as a consequence the existing NHS PbR funding structure does not capture cases of IF and there is no specific funding within this mechanism.

Within the UK very little is known about the financial and resource implications of managing patients with type 2 IF and type 3 IF. It is however clear that these patients have prolonged admissions, often requiring critical care stays. In addition they have complex care requirements and involvement of extend multidisciplinary teams. In recognition of these likely increased costs in 1998 both national centres received centralised funding outside of the PbR mechanisms for managing the both type 2 and 3 IF.

There has been one previous estimate which suggested that each patient with type 2 IF costs £767 per in-patient day, although this is based on only one patient without a clear method of assessment (5). It is therefore likely that Trusts which actively manage a significant volume of type 2 and type 3 IF work are inadequately remunerated. Therefore if a proposed service configuration for type 2 and 3 IF involves establishing regional networks then for it to be successful it needs to be adequately resourced. However there is little robust data to determine the financial costs of providing these services or assessing the gap with current payment mechanisms.

Chapter 3: Aims and hypothesis

The literature reviewed in chapter 2 has demonstrated acute IF is a relatively common problem managed at most acute hospitals. Treatment with PN is widely accepted as best practice, yet there remains considerable uncertainty in the published scientific literature regarding the effect on clinical outcomes, the timing of intervention and levels of feeding in patients who are seriously ill. Much of the trials based literature is difficult to interpret and apply to clinical practice as historically many patients with a definite need for PN were excluded from studies on ethical grounds.

Despite the difficulties in the literature base, guidelines from various national and international bodies have been developed with broadly similar recommendations. The literature review has shown there are little published data assessing adherence to guidelines and outcomes in clinical practice. The largest and most notable study, the recent NCEPOD report, identified significant concerns relating to the indications for treatment and the standards of clinical care.

In addition there is growing recognition that there are a very small but significant number of patients with type 2 IF who pose a challenge to manage due to the wide range of clinical expertise and resource required. The literature review highlights the difficulties in defining these patients and types of surgery in clinical practice, with the consequence of problems assessing levels of clinical activity at a national level.

The clinical problems posed in type 2 IF are often complicated and expert opinion recommends a structured approach to managing the multi-faceted issues. Due to the problems of defining type 2 IF and the relatively small number of cases, the evidence for this approach has largely been assembled piecemeal, with data taken from a variety of other clinical settings. There are no published outcome data specifically relating to all patients who encompass the definition type 2 IF or IF surgery and no existing evidence that demonstrates improved clinical outcomes in specialist centres. Given the long length of hospital stay and extensive resources required to manage these patients the treatment costs are likely to be high, although exact figures are unknown. It is unlikely that the treatment costs are accurately reflected by existing NHS funding mechanisms.

This thesis will therefore assess some these issues by examining the following interrelated hypotheses:

1) Specialist centres delivering high quality care for acute IF on dedicated IF units can improve clinical outcomes.

2) A simple screening test to identify potential patients with type 2 IF would have clinical utility and such a test, combined with the recently proposed classification of IF surgery, could enable a framework for national reporting, audit and potential research.

3) Establishing clinical outcomes and quality indicators in the management of type 2 IF and IF surgery is an important step in improving clinical practice.

4) The cost of treating type 2 IF is very high and institutions cannot recover this from existing NHS funding mechanisms.

This thesis will examine each of these hypotheses by:

1) Assessing quality of care in acute intestinal failure by:

    a. Assessment of the quality of PN care in patients with acute IF in a single specialist centre compared to outcomes reported in the NCEPOD study.

    b. Assessment of the accuracy of PN administration on a dedicated IFU compared to other specialist wards.

    c. Examining changes in the incidence of CRS following the development of a dedicated IFU.

2) Identifying type 2 intestinal failure:

    a. Examining whether classification by the number of days a patient receives PN is a useful screening tool in identifying those with type 2 IF and whether this simple classification has utility in clinical practice.

    b. Determining whether the recently proposed criteria for IF surgery are applicable in a cohort of type 2 IF patients and how this classification could be used in further benchmarking, audit and research.

3) Identifying clinical outcomes and quality indicators in type 2 IF and IF surgery by:

    a. Examining a cohort of patients with type 2 IF to assess the aetiology, classification, length of stay, mortality and clinical outcomes. Identifying aspects of clinical care that could be considered important indicators of quality in demonstrating effectiveness of specialist centres.

4) Determining treatment costs in type 2 IF by:

    a. Analysing health care resource utilisation by a cohort of patients with type 2 IF and comparing to the amount reimbursed to the institution. Alternative mechanisms to fund type 2 IF services within the NHS will be considered.

Chapter 4: Assessing quality of care in acute intestinal failure

As already discussed, acute IF is relatively common in hospitalised patients, predominantly after abdominal surgery. PN is an established intervention, used as a supportive treatment until gut function returns and enteral intake can be resumed. It is however, an invasive and expensive treatment which even in experienced hands can be associated with significant clinical risk of both PN related and non-PN related complications. Despite guidelines from various national and international societies regarding the practical aspects of managing these patients there have been few publications assessing the quality of nutritional care. Recently significant deficiencies in standards of care were identified by an NCEPOD publication assessing PN treatment in hospitalised patients.

In addition to concerns around quality of care, there has been increased recognition that patients with type 2 IF have specialist needs not met within the current structure of the NHS. This has prompted a number of hospitals to develop as specialist IF centres but it is not known whether these units provide a high standard of care or result in improvements in clinical outcome measures.

The series of observational and retrospective studies reported in this chapter were designed to test the hypothesis that specialist centres deliver high quality nutritional care and that developing dedicated IF units can improve clinical outcomes. This was evaluated by:

- Assessing the quality of PN care standards in patients with acute IF in a single specialist centre compared to outcomes reported in the NCEPOD study.
- Assessing the accuracy of PN administration on a dedicated IFU compared to other specialist wards.
- Examining changes in the incidence of CRS following the development of a dedicated IFU.

4.1 A comparison of parenteral nutrition care standards between patients in a single specialist centre compared to outcomes from the NCEPOD study

This study examined the standards of PN care provided in a single specialist IF centre experienced in managing patients with acute IF. These data were compared to results reported by NCEPOD to assess whether the concerns raised in this report were universal, unavoidable or relevant in clinical practice.

4.1.1 Methodology

4.1.1.1 Patient selection

All patients referred for consideration of parenteral nutrition support at UHS were assessed by members of the multidisciplinary NST. Referral was made by the clinical team with responsibility for the overall patient management depending on perceived need. Local guidelines regarding indications and monitoring of PN were well known to potential referring clinicians and widely available in writing.

The NST was made up of clinicians, specialist nurses, dietitians and pharmacists. In the vast majority of cases patients were reviewed prior to starting treatment and a decision was made by the NST in conjunction with the clinical team as to whether PN treatment was appropriate. Rarely patients were transferred from another hospital already receiving PN or were started out of hours by the clinical team and the decision was made by the NST regarding on-going need for PN the next working day.

A standardised data set was collected from each patient by a member of NST. This included basic demographic data; age, gender, ward, consultant, diagnosis, procedural interventions and indication for PN. Details pertaining to central venous access were also recorded where available. All patients were classified by IF subtype, where this was unclear final consensus was reached at the end of hospital stay after multidisciplinary discussion. Where information was not clear from the patient or patients' notes clarification was sought from the clinical team. Details regarding complications were also recorded.

A detailed nutritional assessment was performed for each patient. Body weight was measured where possible, otherwise it was taken from recent documented weights in clinical notes, patient recalled weight or failing that estimated weight by the NST. Height was recorded based on patient recalled height or estimated using measurements of ulna length (91). Percentage weight

loss was recorded based on patient recall where realistic and where possible this was corroborated by documented weights in clinical notes. The number of days the patient had minimal oral intake was also recorded and contributed to the acute disease effect score.

Every patient had their energy requirements estimated using the Schofield equation to predict basal metabolic rate (173). A standardised activity factor of 20% was added to each patient's basal metabolic rate. This relatively low incremental value over basal metabolic rate was used due to concerns relating to the provision of excess energy and protein in patients who were acutely ill and metabolically unstable as previously discussed in section 2.3.3.3.2 (8, 85). A careful assessment of fluid balance, current loses and loses in the in the preceding months was also undertaken.

The majority of patients were given approximately 50% of their estimated requirements for the first 48 hours in line with NICE guidelines (8). Those at higher risk of refeeding complications or those who were considered to be very metabolically unstable were given more cautious initial rates of feeding. The majority of PN was given as standardised triple chamber regimens, with tailored electrolyte and micronutrient additions. Bespoke compounding was available for patients with specific requirements.

All members of the NST were either clinicians or had completed 'Non-medical prescribing courses', enabling independent prescription within their sphere of clinical practice. The decision to provide PN was based upon initial assessment or in cases of uncertainty a more detailed discussion was had with clinicians from the patients' team and the NST. A trial of oral intake, with or without ONS, and close monitoring by the NST was advised if there was doubt regarding the adequacy of gut function. The possibility of using enteral tube feeding (nasogastric, nasojejunal or fistuloclysis) in preference to PN feeding was considered in all cases.

4.1.1.2 Intestinal failure unit transfer

From April 2010 all adult patients who required PN were considered for transfer from their existing location to the 12 bedded IFU. However, due to the limited number of IFU beds, precedence was given to individuals expected to require more prolonged PN support i.e. predominantly Type 2 IF patients and those with established long term PN support needs i.e. type 3 patients. Patients who had care needs which were considered to take precedence over their PN care were not moved, for example those requiring high dependency or intensive care nursing, negative pressure isolation or specialist neurosurgical or orthopaedic care. Transfer was coordinated by the NST. Where immediate transfer was not possible due to capacity issues, patients were added to a waiting list and prioritised according to need.

4.1.1.3 Clinical follow-up

Patients were seen daily (Monday to Friday) by a member of the NST. Clinical outcome measures were recorded on a daily basis on standardised data collection sheets (appendix A). Patients continued on PN until oral or enteral nutrition had been successfully established. The number of days of PN and length of stay were recorded for all patients.

All patients receiving PN underwent careful biochemical and haematological monitoring as part of their routine clinical care recommended by local guidelines, although clinical teams were responsible for determining the frequency of blood sampling. Glycaemic control was assessed with daily near-patient capillary blood glucose measurements every 6 hours for the first 24 hours of nutrition support and at least once daily thereafter.

4.1.1.4 Diagnosis of catheter related sepsis

The diagnosis of CRS was made whenever a patient had clinical symptoms and signs of infection after appropriate investigation in the absence of another source of infection (table 2.6). In patients with type 2 or 3 IF other clinical prompts may also have triggered investigation of possible infection as previously discussed. Written local protocols for investigating CRS were widely available for use by clinical teams (appendix B). The ward on which the patient was managed at the time of infection was recorded. In addition all patients admitted to the IFU from other hospitals or from other clinical areas with an existing central catheter in situ had routine blood cultures taken from the device on admission.

The types of infection were then categorised based on the clinical and microbiological evidence available in keeping with local policies (see table 2.5). In cases where there was doubt advice was sought from a consultant microbiologist.

4.1.1.5 Scope of clinical practice

These studies were undertaken in a large publicly funded acute teaching hospital which provided regional and supra-regional services in many specialities including hepatobiliary surgery, oesophagogastric surgery, gastroenterology, hepatology, urology, neurology, cardiothoracics, haematoncology, gynaecology and oncology, in addition to regional IF services.

4.1.1.6 Assessment of standard clinical care

During an eight week period (December 2010 –January 2011) a prospective audit was undertaken to assess the quality of nutritional care provided. All patients who received PN as part of their routine clinical care were included in the study.

The aim of this study was to compare standards of care at this hospital, with those identified nationally in the NCEPOD report (15). Therefore, data fields used for this study were based on criteria from this report. The data set was modified to remove subjective and opinion based measures in an attempt to reduce the effect of reporter bias. This study was registered with the institutions research and audit department.

4.1.2 Results

4.1.2.1 Demographics

63 patients were referred for PN support during the study period. 13 (21%) were managed with oral or enteral tube feeding as an alternative to PN, therefore 50 patients were included for further assessment. The median age was 62.5 years with a range from 22-93 years, 30 patients (60%) were male. These data are comparable with reported data from NCEPOD; average age 65 years, range 19-95 years.

Table 4.1 Speciality of clinical team treating patients commenced on PN

Speciality	Type of ward			
	IFU	NON-IFU	Total	NCEPOD
	Number of patients (%)	Number of patients (%)	Number of patients (%)	% of patients
Colorectal surgery	9 (18%)	9 (18%)	18 (36%)	17.9%
Hepatobiliary surgery	8 (16%)	4 (8%)	12 (24%)	3.9%
Gastroenterology	4 (8%)	3 (6%)	7 (14%)	7.1%
Oesophago-gastric surgery	2 (4%)	3 (6%)	5 (10%)	5.6%
Oncology	0 (0%)	3 (6%)	3 (6%)	2.3%
Cardiothoracic	0 (0%)	2 (4%)	2 (4%)	<1%
Urology	1 (2%)	1 (2%)	2 (4%)	2.1%
Vascular surgery	0 (0%)	1 (2%)	1 (2%)	2.1%
General surgery	0 (0%)	0 (0%)	0 (0%)	22.1%
Intensive care	0 (0%)	0 (0%)	0 (0%)	19.7%

4.1.2.2 Speciality of clinical team

Colorectal surgery referred the largest number of patients requiring PN (36%), a significant number of patients were managed by the hepatobiliary surgical team (24%) (table 4.1). This differs from findings in NCEPOD where the majority of patients were under the care of general surgeons or intensive care. 84% of all patients in this study were managed by teams specialising in abdominal pathology, a similar finding to NCEPOD.

The majority of patients in this study had type 1 IF (74%). However, since the hospital provides regional IF services, there were a larger proportion of patients with type 2 (18%) and type 3 (8%) IF which, may have influenced some demographics and outcomes. Patients with type 2 IF were

predominantly managed by the IF team, with a colorectal lead, although one patient was primarily under the care of the hepatobiliary surgeons. All the patients with type 3 IF were managed by gastroenterologists.

4.1.2.3 Indications for parenteral nutrition

Despite the differences in patient cohorts, the indications for PN were broadly comparable with NCEPOD data (table 4.2). Ileus and obstruction were the most frequent indications for commencing PN. In this study there was probably a greater proportion of patients with enterocutaneous fistulae than would be seen in most hospitals nationally due to the increased proportion of patients with type 2 IF. The most obvious differences between the indications reported nationally by NCEPOD and those identified in our patient cohort were the number of NCEPOD patients given PN for 'failure of enteral nutrition' and where no indication was recorded.

Table 4.2 Indications for commencing PN

Indication	Type of ward			NCEPOD
	IFU	NON-IFU	Total	NCEPOD
	Number of patients (%)	Number of patients (%)	Number of patients (%)	Answers may be multiple
Ileus	10 (20%)	8 (16%)	18 (36%)	115
Obstruction	7 (14%)	5 (10%)	12 (24%)	119
Fistulae	4 (8%)	4 (8%)	8 (16%)	48
Chemotherapy	0 (0%)	3 (6%)	3 (6%)	6
Malabsorption	2 (4%)	1 (2%)	3 (6%)	23
Perforation	0 (0%)	3 (6%)	3 (6%)	91
Short bowel	1 (2%)	1 (2%)	2 (4%)	22
Failure of EN	0 (0%)	1 (2%)	1 (2%)	109
No indication	0 (0%)	0 (%)	0 (0%)	73
Other	0 (0%)	0 (0%)	0 (0%)	506

(data from NCEPOD are illustrated for broad comparison)

4.1.2.4 Ward on which parenteral nutrition initiated

The ward acuity on which the patient first commenced PN differs from the NCEPOD findings (e.g. general surgical ward-level 1 , high dependency unit – level 2 or intensive therapy unit – level 3). In this study a greater proportion of patients started PN in level 1, with a significantly lower proportion of our patients starting in intensive therapy unit settings than NCEPOD (Figure 4.1). The reason for this difference is difficult to ascertain from the data, especially with limited details available from the NCEPOD study. The most obvious difference is that this study was performed

in a single centre and it appears likely that a greater proportion of patients were receiving tertiary centre treatment, as suggested in table 4.1. This may suggest that the nature of the complications arising from more complex surgery may be different compared to patients in secondary care. Although there is no data to support this assumption. Other possible explanations include a more conservative approach to PN in ITU in this centre, which may be influenced by the presence of a nutrition team pharmacist on every ITU ward round. There was also a high proportion of patients with type 2 and 3 IF who were receiving PN treatment outside of critical care.

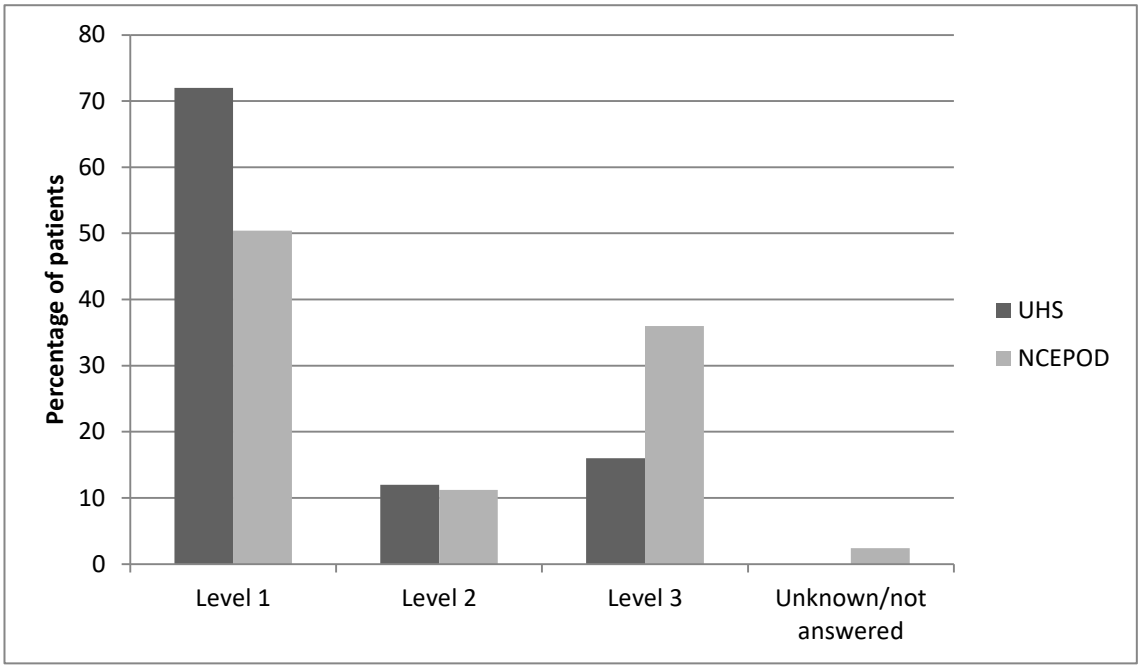


Figure 4.1 Ward level where PN first commenced

Level 1=general ward, level 2=high dependency unit and level 3= intensive therapy unit.

4.1.2.5 Day of the week parenteral nutrition commenced

The majority of PN (80%) was started on a weekday, in keeping with NCEPOD findings (84%). However it was felt this question was not necessarily representative of the decision making process regarding PN initiation nor indeed demonstrated the point that out of hours PN was rarely indicated. In a scenario where a decision was made to commence PN on Friday afternoon it would be unreasonable to then wait until the following Monday, therefore a tailored PN regimen was prescribed for the following day, Saturday, rather than commence a generic emergency regimen. Therefore the patient started treatment on Saturday but in a planned manner. A more

useful question in the NCEPOD study would have been “which days of the week did unplanned PN begin”.

Five of our patients (10% of total) started unplanned PN out of hours, all of which occurred on Saturday or Sunday, 3 were appropriate indications and started on what could be justified as an appropriate day according to need and indeed continued PN treatment (figure 4.2). However, it is unlikely that the clinical outcome would have been altered by delaying treatment until the next working day and almost without exception PN should not be commenced as an emergency treatment. Two of these five (4% of total) were deemed inappropriate with regard to indication and were stopped on the next working day, compared to 29% in the NCEPOD study. One of these two inappropriate cases was an uncomplicated post-operative ileus, the other was an inpatient with type 2 IF already receiving daily input from the nutrition team and IF surgeon. Therefore in agreement with the NCEPOD data inappropriate PN use is more likely to occur out of hours and reflects the lack of access to the NST and expertise out of hours.

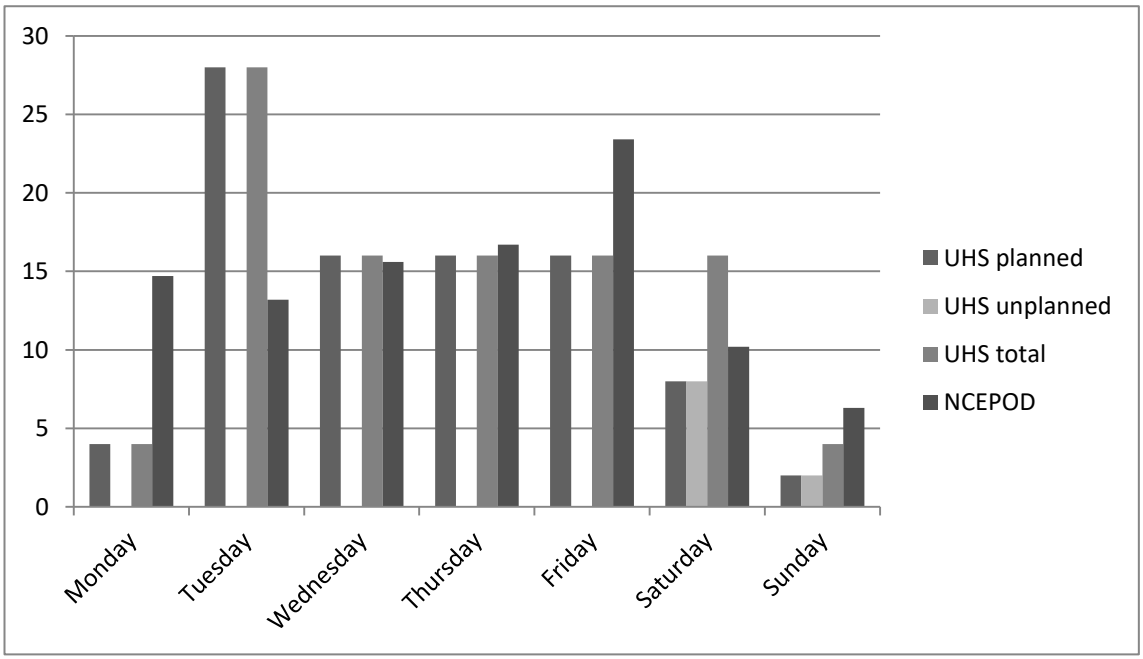


Figure 4.2 Day of the week PN commenced

4.1.2.6 Decision making

A member of the NST started or was involved in the decision to start PN in 90% of cases, compared to 52.7% of patients nationally. The 10% of cases in which the NST were not directly involved in the decision making process all occurred outside normal working hours. The decisions

to commence PN out of hours were taken by doctors, 3 of the 5 in critical care settings. All of the doctors were specialist registrar grade with or without consultant in-put.

4.1.2.7 Enteral nutrition

In this study the majority of patients (66%) had attempted some form of enteral nutrition prior to commencing PN, this is a slightly higher percentage than found nationally (52%). Only a small percentage of patients had an attempt at enteral tube feeding prior to PN (table 4.3). On review of these cases, the majority relate to high nasogastric tube loses combined with absent bowel movements indicating persistent ileus or obstruction, a non-functioning GI tract, therefore limited prospect of effective enteral nutrition.

Table 4.3 Types of enteral nutrition treatment used prior to commencing PN.

Type of Enteral feeding	UHS (%)	NCEPOD (%)
Oral +/- ONS	29 (58)	272 (20)
Nasogastric	1 (2)	246 (18)
Nasojejunal	3 (6)	30 (2)
None	13 (26)	642 (48)
Unknown	4 (8)	30 (2)
Other	0	112 (8)
Total	50	1332

In those patients without any enteral feeding prior to starting PN, data regarding the number of days with no nutrition was available in 12/13, 1 patient was transferred from another hospital without this data being available. The mean number of days with no 'meaningful' nutrition was 9.1 (range 0-12), compared to 7.5 days nationally. These data combined with the increased proportion of patients who were tried on enteral alternatives implies that alternative options were pursued by both clinical teams and the NST before PN was instigated.

Despite this increase in time without nutrition compared to national data, when these cases were reviewed by members of the NST, in none of the cases was this felt to be a delay in recognition of the need to start PN. Indeed, in all of the cases, the patients had been referred at an earlier stage by the clinical teams and then were being monitored by the NST. In the majority of these 12 patients PN was commenced for unresolved ileus.

Once the decision to start PN had been made 5 patients waited longer than 24 hours to start treatment. This was felt to be reasonable in 4 of the of the 5 patients, where an elective decision at the time was taken to wait longer and establish central access via a PICC rather than opt for earlier feeding via a temporary CVC. In 1 patient it was felt to be unreasonable due to delays in obtaining central venous access and their clinical need. Only 1 patient waited more than 48 hours, again due to delays establishing venous access.

The mean duration of treatment in this study was 19.2 days, compared to 12.2 seen in national data. However, if the patients are grouped by category of IF and then the average for patients with type 1 IF is broadly similar to NCEPOD data (table 4.4). In this study 9 patients (18%) received PN for more than 30 days compared to 7% nationally.

Nine patients in this study received PN for 3 days or less (18%) compared to 16% in NCEPOD data. 6 of the patients were assessed as high or moderate risk of refeeding complications, predominantly based on the duration of days without nutrition, but were able to quickly establish oral intake. Two patients were commenced out of hours and stopped by the NST on the next working day, the other had significant graft versus host disease and developed sepsis and the PN was stopped on day 3.

NCEPOD expressed concerns regarding patients who received less than three days PN. Whilst this was the case in two patients who were started inappropriately, the decision in 7 of the patients was based on local and national guidelines.

Table 4.4 Types of intestinal failure and duration of PN treatment

	NCEPOD	**UHS (All patients)**	**Type 1 IF**	**Type 2 IF**	**Type 3 IF**
Mean days of PN	12.2	19.2	13.5	40.7	23.8
Median days of PN	8	12	9	39	13
Range	1-276	1-96	1-57	1-96	1-69
Number receiving 3 days or less	177	9			

4.1.2.8 Appropriateness of prescription

All the initial PN regimens in this study were multi-chamber bags with added micronutrients and tailored additions. This is the standard PN available within the hospital, all out of hours bags have added multivitamins and therefore ensure compliance with NICE guidelines (8). In contrast

NCEPOD findings suggest micronutrients were not routinely administered in 43% of patients. 90% of prescriptions were signed by a member of the NST, the patients started out of hours were signed by a doctor.

Nutritional assessment was felt to be adequate in only 46% of patients in the NCEPOD study. In this study all the patients (90%) seen by the NST had documented nutritional assessment, requirements and biochemical review prior to treatment. In those not seen by the NST prior to treatment all had a documented weight assessment and biochemical screen but none had any further assessment. However in all the cases where PN was started out of hours the prescription adhered to the local guidelines. Micronutrient status forms part of the NST assessment process but in no patients was it formerly measured. Refeeding risk was documented for all patients at high risk.

4.1.2.9 Nutritional monitoring

Objective assessment of adequacy of monitoring was difficult in this study and open to bias. The NCEPOD study commented on numerous parameters regarding monitoring including; biochemical review, weight, prescription review, glucose, fluid status, vascular access, clinical status and anthropometric measurements. To remain objective, assessment of monitoring was limited to biochemical review recording in the first week.

A baseline weight was recorded for all patients in this study, in the NCEPOD data a weight was not recorded in 240/738 (32.5%). The fluid balance charts were fully completed in 44 (88%) patients, and partially completed in 6 (12%) patients. There were deficiencies in the biochemical assessment of 18 (36.0%) patients as they did not have daily biochemical monitoring. In the NCEPOD study 43.3% of patients were reported to have had inadequate monitoring. Blood glucose measurements were adequately monitored in 35/42 (83%) cases. Patients commencing PN in ITU were excluded as glucose monitoring is included in blood gas samples taken for alternative reasons. There were no episodes of refeeding syndrome in this study however, in the NCEPOD study 33 cases in 877 patients (3.8%) were identified. Interestingly the NCEPOD study reported 174 patients were documented to be at high risk of refeeding syndrome, 19% (33/174) went on to develop the syndrome, despite adequate precautions being taken in 20 patients.

4.1.2.10 Care of central venous catheters

The commonest catheter used for PN administration in this study as in NCEPOD was a short term central venous catheter. However the proportion of patients with this type of device was significantly lower 44% compared to NCEPOD 73%, with a greater proportion of PICCS and tunnelled catheters used (see table 4.5). Multi-lumen catheters were predominantly used due to

the nature and number of infusions needed. Invariably a lumen was reserved specifically for PN but this was not clearly documented in the notes. The documentation of the tip position was generally poor with the exception of PICCS, which in the main were placed by the vascular access team. It is unclear from the data whether tip position documentation for CVCs relates to substandard documentation or care. Regardless it is an important finding. In the NCEPOD study tip position was documented in 45.5% of patients. Documentation around tunnelled catheters appeared to be poor, however several of these were placed either at other institutions or several years ago, with no access to notes at the time of the study.

There were only 2 complications in this study, both of which were catheter related sepsis. One patient developed a catheter related blood stream infection and the other a catheter suspected blood stream infection, both of these occurred in temporary CVCs. Data from the NCEPOD study report suspected or confirmed catheter infections in approximately 15% of patients.

Table 4.5 Initial mode of PN delivery

	Site of Insertion documented		**Type of catheter**		**Tip position documented**		**Designation of operator**				**Complications**
Device	Yes	No	Multi lumen	Single lumen	Yes	No	Anaesthetist	CNS	Radiologist	Unknown	
Temporary CVC	20	2	22	0	0	22	18	0	0	4	2
PICC	21	0	17	4	17	4	1	18	1	1	0
Tunnelled CVC	3	3	3	3	1	5	3	0	0	3	0
Port	0	1	0	1	0	1	0	0	0	1	0

4.1.3 Discussion

In this study, data were recorded prospectively compared to the retrospective nature of the NCEPOD study. This enabled real time clarification of uncertainties and ensured more accurate data recording. However one of the main weaknesses was the inability to give an unbiased view when it came to questions requiring “expert opinion”, as the author was both a core member of

the NST and designed and collected data for the study. Therefore these types of questions posed by NCEPOD were steered away from.

The demographics of this study population were broadly similar to those seen in NCEPOD. General surgery in this institution has largely been replaced by sub-specialisation, as in many teaching hospitals which explains why in this study no patients were under a 'general surgeon'. In this study patients who required PN support whilst in level 2 or level 3 care were also recorded as the speciality of the clinical team rather than ITU.

Post-operative ileus accounted for 36% of indications for PN in this study. Direct comparisons with NCEPOD data were not possible as they reported multiple answers. However in both studies it was the most frequent indication. The indications identified in this study are similar to NCEPOD and those reported by Hvas et al in a similar study from a UK teaching hospital (130).

A common finding in the NCEPOD data was the number of patients where there was no documented indication. This may in part be a reflection of the difficulties of retrospective paper based studies where details about decisions taken at the time may have been poorly recorded. However combined with the fact that in 29% cases experts felt PN was not indicated, it suggests poor clinical decisions were commonly being made with regard to assessment and documentation. It may also indicate limited understanding of the benefits, risks and costs involved with PN.

The overwhelming majority of patients (90%) in this study had a planned start day for commencing PN with assessment by a member of the NST. There are very few instances when starting PN out of hours will be indicated and best practice should be to wait until the next working day. However, if required in exceptional cases, there should be an out of hours policy to reduce the risks, which in the case of this institution requires agreement by the on call pharmacist. Basic nutritional assessment i.e. weight and BMI has to be performed and electrolytes need to be reviewed before the PN can be dispensed. Rates of infusion are also limited to reduce the potential for refeeding syndrome. All out of hours bags in this hospital have added micronutrients and intravenous vitamins should be prescribed as per policy.

As in NCEPOD, in those who started unplanned PN out of hours there was a much higher proportion of cases where there was no clear indication and hence PN use was inappropriate. In this study 5 patients commenced unplanned treatment, 2 of which were deemed inappropriate. Despite attempts to control out of hours PN, decisions will always need to be made by clinicians in emergency situations. The only instance this will change is by providing a 7 day NST service, which would have a huge resource implication across the NHS.

The NCEPOD study also raised concerns that a high number of patients received PN for less than 3 days, suggesting it was a marker of poor PN care. There is no evidence to support this as an objective indicator of PN care. The origins of this statement arise from the Veterans affairs study where hypercaloric PN was prescribed routinely preoperatively and for 3 days postoperatively regardless of whether patients really needed it. In those who were only mildly malnourished there were no differences in non-infective complications but there was an increase in infective complications (14.4% versus 3.7%; p=0.004; relative risk 3.86 95% confidence interval 1.48-10.08) (93). These data have subsequently been used by some authors to suggest that receiving less than 3 days of PN is a marker of poor nutritional care but actually the methodology in this study is not relevant to current clinical practice and illustrates the misunderstandings that arise from the limited PN studies available.

It is inevitable that a proportion of patients will receive PN for less than 3 days. This criterion should not be used as a PN quality indicator in isolation, although in the context of the other NCEPOD study findings it does suggest issues with decision making. The concern of highlighting this as an objective indicator of PN care is that many patients with prolonged post-operative ileus or early post-operative small bowel obstruction tend to see restoration of intestinal function around 5-10 days post-operatively. UK guidelines recommend 'nutrition support should be considered in patients who have eaten little or nothing for more than 5 days and/or are likely to eat little or nothing for the next five days' (8). Therefore it is likely there will always be a cohort of patients who receive a short duration of PN. However, in combination with other criteria assessing overall standards it may highlight the need for a more detailed review of practice.

A small sub-group of patients in this study waited 9 days before commencing PN. In this sub-group the patients had been carefully assessed and monitored, there were no other nutritional risk factors and were considered to have realistic chances of not requiring PN. This time period is longer than some experts would recommend but, as discussed in the literature review, there is no hard evidence on when to instigate PN. Guidelines recommend that nutrition support is provided for 'at risk patients' after more than 5 days without nutritional intake. However the benefits of this approach may be offset by the relatively high level of complications associated with PN. This balance of risks and benefits is more relevant in patients who have undergone abdominal surgery, where self-limiting post-operative ileus is a relatively common occurrence and this approach would likely result in significant over treatment in those without other nutritional risk factors.

In this study there were deficiencies in biochemical monitoring, albeit to lesser extent than reported in NCEPOD. This is in part explained by the nature of the NST service, which acts as an advisory service and therefore is not completely responsible for ensuring that additional

biochemistry (magnesium and phosphate) were undertaken. Ultimately it comes down to team working and communication with the clinical teams managing these acutely unwell patients.

The criteria for defining a metabolic complication in the NCEPOD study were not well defined. It appeared to be largely based on the occurrence of an abnormal reading of phosphate, potassium, magnesium or sodium. Whilst they recognised that these abnormalities cannot always be prevented it seems presumptive to report these as 'complications' as many critically unwell patients develop significant electrolyte disturbance in the absence of PN and the study was not designed to demonstrate this. The more significant finding in the NCEPOD study was the occurrence of refeeding syndrome. Although there was no consensus definition, expert opinion felt it occurred in 33 patients, despite adequate preventative precautions being taken in 20.

In this study in keeping with the NCEPOD findings there was evidence of poor documentation with regard to catheter insertion with the exception of PICCs which were performed by the vascular access team. In this institution local policy enables CVCs to be accessed for other uses, providing that there is a dedicated lumen for PN. In contrast NCEPOD felt this represented poor practice, this is despite European guidelines recognising that a dedicated lumen in a multi-lumen CVC was accepted practice (137). Catheter infections will be discussed in more detail in section 4.3.

In summary, there were significant methodological differences between this study and NCEPOD, in addition to limitations regarding outcome measures that required an expert opinion or judgement. However, this study has shown that standards of PN care in this centre generally would be regarded as good, particularly with regard to assessment and decision making. Deficiencies were identified predominantly with aspects of biochemical monitoring and components of catheter care, although these largely fall outside of the immediate control of the NST. However part of the role of the NST is to engage ward staff and junior doctors in the care of these patients helping them to recognise why it is important to improve standards and identify mechanisms through which this can be achieved.

4.2 Accuracy of parenteral nutrition administration in patients in a dedicated intestinal failure unit compared to non-specialist wards

Identifying objective measures of quality of care in acute IF that might result from setting up a dedicated IF unit poses a number of challenges. This is in part due to the diverse nature and complexity of the patient cohort which make overall changes in clinical outcomes difficult to interpret, especially as standards of individual elements of care such as those related to nutrition

only contribute to a relatively small part of the overall patient management during their hospital stay.

Nevertheless, administration of intravenous fluids and PN and the careful recording of fluid balance are important components of good IF practice, particularly in type 2 IF where treatment maybe very prolonged and in clinical trials of nutritional intervention difficulties ensuring patients receive the correct amount of the artificial nutrition prescribed are frequently reported due to problems such as interruptions from various medical interventions, surgery, problems with intravenous access, nasogastric tube placement and variable intestinal function. This study was therefore designed to test the hypothesis that as a consequence of improved training and knowledge of the nursing staff on a dedicated IFU, standards of PN administration and recording would be improved compared to those on non-IFU wards.

4.2.1 Methodology

Checks of the accuracy of PN administration against prescription were made using considerations driven by standard hospital policies. It is standard practice that all bags of PN dispensed from pharmacy are labelled with an infusion rate recorded in millilitres per hour to one decimal place. A total infusion volume per 24 hours is also recorded to one decimal place. The patients' prescription which contains the same information accompanies the PN bag in order for nursing staff to administer the drug. The hospital policy then states that when PN is connected both the infusion rate and total volume are programmed into the bedside infusion pumps. The nursing staff then record the start times, hourly infusion volume and finish times on the fluid balance charts. Where infusions are suspended these details are also recorded.

During a 2 week study period all bags of PN (including the incorporated intravenous giving) sets released by pharmacy were weighed. This was performed at the end of production by specialist aseptic pharmacy technicians using the same set of calibrated scales. The PN was transported to the ward and administered by the ward nurses via infusion pumps as per standard practice. At the end of the PN infusion the bag was then capped and stored on the ward in a dedicated study box. Each bag was then collected and taken back to pharmacy, where they were reweighed. Ward staff were informed of the study but were not aware of the purpose.

In order to calculate the administered volume, the weight of PN that the patient received was used. An experiment was conducted to ascertain the specific gravity of standard triple chamber bags. 5ml of solution was measured using a Biohit Proline Plus pipette set to 5.0 ml, using a forward pipetting technique and a recently calibrated Sartorius BL310 balance. Precision and accuracy checks were performed on this pipette set to this volume by means of multiple

weighings of water (a minimum of 10). These were evaluated using a Microsoft Excel spreadsheet to give coefficients of variation for the pipette performance (precision and accuracy were within the 1% target) and to determine the actual volume of water measured by the pipette (mean (x) = 4.943). Multiple 5 ml weighings of PN were performed (5 for each sample) to give a mean value for each sample (y). Samples were taken from five different bags of PN, with their components noted. The specific gravity (SG) for each sample was calculated using the formula: SG = y / x. The SG of the five samples ranged from 1.024 – 1.060, with a mean SG of 1.0428. This mean SG was used to convert the weight of PN the patient received to the administered volume (volume=mass/SG).

Data were collected from patients treated throughout the hospital and recorded on standardised data collection forms during the 2 week study period (appendix C). Subjects from intensive therapy unit and those receiving bespoke compounded PN regimens were not included in the study. To establish the accuracy of administration patients who had a recorded interruption to the PN were excluded. PN bags in which an incomplete set of measurements were not recorded were also excluded. This study was registered with the institutions audit department.

4.2.2 Results

Data from the administration of 224 bags of PN were collected, 184 episodes (82%) were from patients being managed in the IFU. A further 40 episodes (18%) were from a variety of wards, urology (17) general surgical (14), surgical HDU (5) and general medical (4). The mean volume of PN prescribed in a 24 hour period was 2057mls, with patients on the IFU being prescribed 359mls greater than those on non-IFU wards ($P<0.001$). The mean volume of PN administered to patients was 2159mls (table 4.6).

Table 4.6 Administration of PN by clinical area

	IFU	**Non-IFU**	**p value†**
N	184	40	
Volume of PN prescribed (mean (sd))	2122 mls (493)	1763 mls (288)	<0.001
Volume of PN administered (mean (sd))	2218mls (570)	1891 mls (328)	<0.001
Volume of PN recorded (mean (sd))	2125 mls (545)	1737 mls (303)	<0.001

sd standard deviation †student's t test

These results demonstrated that there were significant differences between the two cohorts with regard to the volume of PN prescribed, despite the small number of patients in the non-IFU group. Whilst undoubtedly there were small differences in individuals prescribing habits, the majority of PN was prescribed by two members of the NST with a similar practice, who prescribed for patients in both clinical areas. It therefore seems more likely that the differences are explained by differences in the patient cohorts.

Table 4.7 Proportion of PN administered by nursing staff to patients by clinical area

	All patients	**IFU**	**Non-IFU**
Difference between prescribed and administered volume (mean (sd))	102 mls (197)	96 mls (208)	129 mls (137)
Percentage difference between prescribed and administered volume (mean (sd))	4.9% (10.2)	4.3% (10.6)	7.4 % (8.2)
Minimum and maximum difference between prescribed and administered volume	47.7%-132.1%	47.7% - 117.4%	80.9% - 132.1%

sd standard deviation

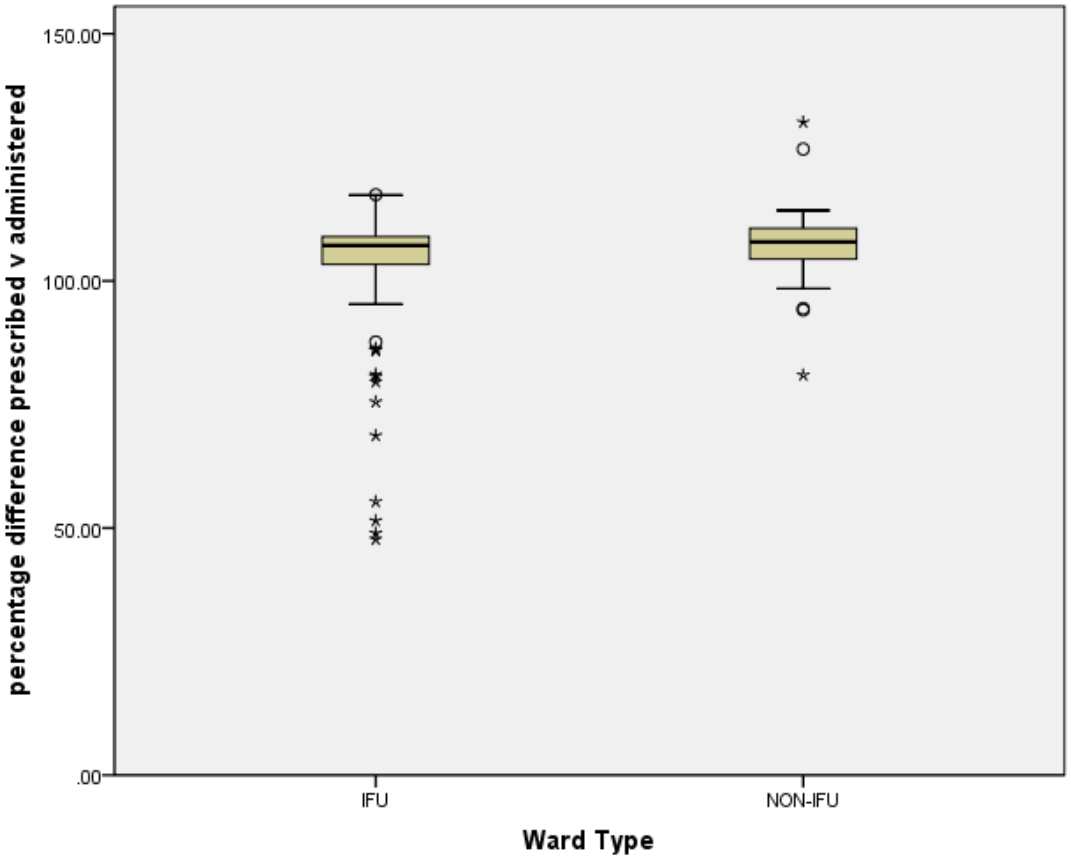


Figure 4.3 Proportion of PN prescribed compared to administered volume

○ Outlier; ≥1.5 IQR from either end of IQR *Extreme; ≥3 IQR from either end of IQR

On average patients throughout the hospital received more PN than was prescribed, those on non-IFU wards received proportionally more than those on the IFU, 7.4% v's 4.3% (table 4.7 and figure 4.3). Regression modelling demonstrated that this difference was significant. The standard deviation and spread of data were noticeably larger in the IFU group (table 4.8).

Predicted difference between prescribed PN volume and the volume of PN administered.

= -0.19 (administered volume) + 95.26 (IFU status) +235.79

Table 4.8 Regression modelling between prescribed and administered PN volumes

Variable	Coefficient	95% Confidence Interval	Significance
Administered volume	-0.19	-0.234 , -0.151	<0.001
IFU Status	95.26	35.525, 155	0.002

(IFU status; IFU=1, non-IFU=0)

Table 4.9 Proportion of PN received by patients recorded in clinical notes compared to actual administered volume by clinical area

	All patients	IFU	Non-IFU
Difference between recorded volume and administered volume (mean (sd))	104 mls (252)	93 mls (257)	155 mls (224)
Percentage difference between recorded and administered volume (mean (sd))	5.9% (12.8)	5.1% (12.0)	9.9% (15.3)
Minimum and maximum differences between recorded and administered volume	49.0% - 168.9%	49.0%- 164.5%	79.3% - 168.9%

sd standard deviation

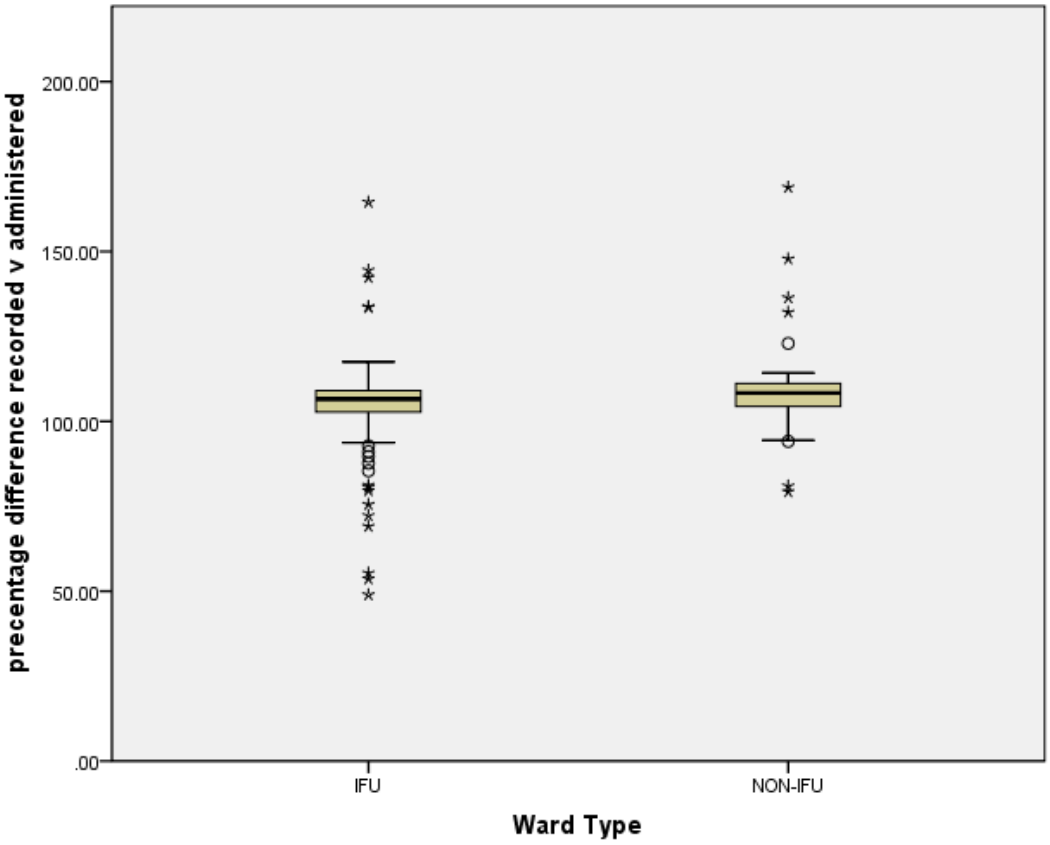


Figure 4.4 Proportion of PN recorded versus administered

○ Outlier; ≥1.5 IQR from either end of IQR *Extreme; ≥3 IQR from either end of IQR

Similar findings were also identified when comparing the volumes of PN recorded in the patients clinical notes compared to volumes administered, patients received more PN than was recorded on fluid balance charts (table 4.9 and figure 4.4). There was a significant difference between IFU and on non-IFU wards when assessed with regression modelling (table 4.10).

Predicted difference between recorded PN volume and the volume of PN administered

=-0.155 (administered volume) + 112.029 (IFU status) +138.106

(IFU status; IFU =1, non-IFU=0)

Table 4.10 Regression modelling between recorded and administered volumes

Variable	Coefficient	95% Confidence Interval	Significance
Administered volume	-0.155	-0.214 , -0.096	<0.001
IFU Status	112.029	-27.836, 196.221	0.009

4.2.3 Discussion

Many more results were available from IFU than non-IFU wards. In part this was due to the number of patients treated in the IFU but there was also a significant limitation in engaging nurses on the non-IFU wards in the study so that they did not discard the remainder of the PN once the infusion was finished. This was despite attaching specific labels to the bags and providing collection points. As a result the sample size from non-IFU wards was smaller than anticipated and may have introduced sampling bias when comparing the two sets of data.

Despite the use of automated pumps with programmable hourly infusion rates and total infusion volumes there were statistically significant inaccuracies in PN administration. On average patients received 5% more PN than prescribed, which probably had little if any meaningful clinical effect. However the spread of these data is of note, approximately 68% of patients lie within one standard deviation of the mean, receiving between 95 to 115% of their prescribed volumes, with 32% falling outside this range.

This study demonstrates that there are cases of significant over and under provision of energy, protein, electrolytes and fluid to individuals who are often metabolically unstable, which could be potentially serious. In the majority of patients these inaccuracies of PN administration are unlikely to have serious consequences, as even a 25% increase in PN volume is only a relatively modest change in nutrient provision for a 24 hour period. However, if these inaccuracies were repeated over a sustained period it may have a clinically more significant effect, although this study did not assess this.

This study demonstrated that the accuracy of PN administration was significantly better in a specialist unit. This is unsurprising given that nurses from the IFU have a greater experience, engagement and training in IF and PN administrations compared to non-specialist ward areas. The study did not formerly examine the reasons for the inaccuracies in drug administration and recording, however it is likely that they are multifactorial and even with very intensive nurse to

patient ratios they could not be completely overcome. There was also a significant difference in the sample sizes between IFU and non-IFU data which may have biased the results.

Informal discussion with the nurses following the study revealed the most likely explanation for the minor differences between prescribed and administered volumes was that the total infusion volume limit was commonly not set at connection, meaning the pump will continue to run after the 24 hours has expired. This is important as most patients receive a proportion of a fixed size bag over 24 hours and there is the potential for the infusion to overrun. This is a simple change in clinical practice which was subsequently implemented following the study.

There were a small number of infusions where the administered and recorded volumes were significantly different. The reasons behind this were not examined in this study but clearly raise cause for concern. It was not possible to assess in more detail at the time without unblinding the nurses to the purpose of the study. Technical difficulties with fluid administration are common and in the main can be overcome by adjusting subsequent prescribing to take this into account. However it is only possible to do this when fluid balance charts are accurately completed.

This study demonstrates inaccuracies of PN administration throughout the hospital, however significant differences were demonstrated between IFU and non-IFU wards. Whilst in the majority of cases these relatively small errors will have little clinical effect, there were a proportion of infusions which could have been potentially harmful. Significant improvements could be made by using existing equipment correctly, such as setting the total infusion volume, to eliminate minor infusion problems. However, there also needs to be a focus on education and training regarding the importance of accurate recording on fluid balance charts. These findings may also serve as an indicator to highlight the accuracy of other intravenous infusions such as fluids and drugs. These findings should be investigated further with a prospective study correlating fluid administration and recording to individual patients clinical data.

4.3 Changes in catheter related sepsis rates following the development of a specialised intestinal failure unit

Catheter related sepsis is a recognised complication of PN treatment that is associated with increased morbidity and mortality. Even the suspicion of CRS interrupts PN treatment and a confirmed diagnosis is associated with increased healthcare costs. As described in the literature review, there are multiple factors that contribute to increased levels of infection. Low rates of CRS have long been associated with good standards of PN care and indeed data from the NCEPOD

study raised concerns regarding high levels of infection seen in many patients. It is unknown whether managing patients on an IFU results in a reduction in CRS.

This study was designed to assess in further detail the incidence of CRS in hospitalised patients receiving PN. It assessed indication, nutritional status, type of catheter, appropriate investigations and causative organisms and their effect on rates of infection based on prospective data collected as part of routine clinical practice.

Due to the observational nature and prolonged duration of this study and the fact that there were no significant changes to clinical practice with regard to catheter access techniques or policies for investigating CRS during its duration it was possible to compare changes in CRS rates that occurred before and after the introduction of an IFU.

4.3.1 Methods

4.3.1.1 Patient selection

All patients receiving PN who had a possible episode of CRS were recorded on the NST database. Data were recorded prospectively between 6th April 2009 and 5th April 2011. Patients who developed CRS on intensive care were excluded from the study.

4.3.1.2 Data collection

Data collection included admitting speciality, nutritional status, PN indication, catheter type, causative organism where known, requirement for intensive care, length of stay and mortality.

Infections were categorised depending on if they occurred before the IFU or after the IFU was established (April 2010). Those patients treated after April 2010 were also grouped into IFU and non-IFU wards. In those patients who developed an infection within 24 hours of moving wards the infection was attributed to the transferring ward. All patients who stopped PN were followed up for a minimum of 24 hours.

4.3.1.3 Interventions

From April 2010 regular education sessions to ward staff on the IFU were provided by lead IFU nurses regarding importance of CRS, potential causes and preventative measures. In addition all nurses on the IFU undertaking any connection on central catheters had additional training in the standard aseptic techniques which were utilised throughout the hospital. An assessment of competence prior to being able to undertake these procedures independently was also performed. This intervention was not provided for nurses in other wards.

At the outset of the IFU opening monthly meetings were set up to review the IFU activity which incorporated a retrospective review of all potential CRS cases and where that episode occurred on the IFU a route cause analysis was also undertaken.

4.3.2 Results

4.3.2.1 Patient demographics

There were 47 episodes of CRS between 6th April 2009 and 5th April 2011. There were no differences between the age and gender distributions in those who had CRS and those who did not (table 4.11). The nutritional status and proportion of patients admitted as an emergency were also similar in both groups. Patients who had an episode of CRS had a significantly longer median length of stay compared to those who did not (38 versus 26 days, p<0.001), although there were no differences in the proportion of patients who required a ITU admission during their stay (40% versus 31%, p=0.175).

Table 4.11 Demographics of patients with and without catheter related sepsis

	Catheter Related Sepsis	**No Catheter Related Sepsis**	**P value**
N	47	469	
Age (median (IQR))	65 (52-75)	63 (49-74)	0.565†
Gender (M:F)	28:19	254:215	0.477‡
MUST (median (IQR))	2 (2-4)	2 (2-4)	0.732†
Emergency admission (%)	23 (49)	259 (55)	0.409‡
Length of stay (days) (median (IQR))	38 (22-84)	26 (17-43)	<0.001†
ICU Admission (%)	19 (40)	144 (31)	0.175‡
Type 1 IF (%)	34 (72)	375 (80)	0.219‡

IQR interquartile range, ‡ Chi-Square, †Mann Whitney U

The admitting team responsible for the patient and information as to whether the admission event was related to management of cancer is combined to form an admission category and is

presented in Figure 4.5. A high proportion (30%) of patients with urological cancer who received PN developed CRS (8 of 27 patients), these patients were all managed on the specialist urology ward. The most frequent indication for PN was an ileus with obstruction being the second most common indication, other indications are described in table 4.12. The distribution of indications is similar between the two groups.

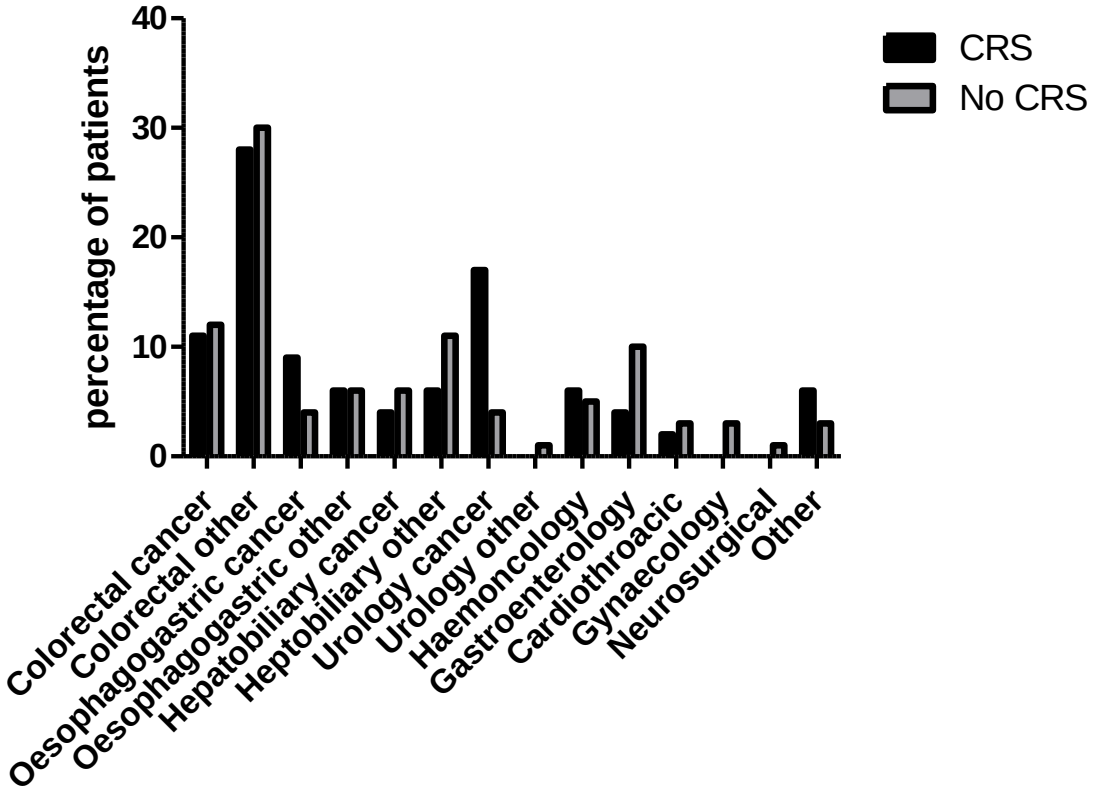


Figure 4.5 Category of admission

Table 4.12 Indication for PN

	Catheter related sepsis (%)	**No catheter related sepsis (%)**	**Total (%)**
N	47	469	516
Anastomotic leak	2 (4)	2 (0.4)	4 (1)
Ileus	17 (36)	187 (40)	204 (40)
GI obstruction	10 (21)	74 (16)	84 (16)
Fistulae	8 (17)	26 (6)	34 (7)
GI perforation	2 (4)	37 (8)	39 (8)
GI dysfunction	2 (4)	23 (5)	25 (5)
Short bowel	3 (6)	38 (8)	41 (8)
Pre-operative nutrition	0 (0)	17 (4)	17 (3)
Mucositis	0 (0)	23 (5)	23 (4)
Post-operative nutrition	0 (0)	13 (3)	13 (3)
Malabsorption	0 (0)	10 (2)	10 (2)
Other	2 (4)	10 (2.1)	12 (2)
Not Documented	1 (2)	9 (2)	10 (2)

4.3.2.2 Intestinal failure unit vs. non-intestinal failure unit catheter related sepsis rates

There was no difference in the median age of patients pre-IFU compared to post IFU (p=0.734). However, patients on the IFU were younger compared to those on non-IFU wards (p=0.023). There were no differences in length of stay between those between the pre and post IFU groups (p=0.303) or when analysed between IFU and non-IFU groups (p=0.563). Although there was a higher proportion of patients admitted to ITU in pre-IFU group (52%) compared to the post-IFU group (22%), this did not reach statistical significance (p=0.068). There were no differences in the

number of patients with type 1 IF and non-type 1 (type 2 and 3) between the pre and post-IFU groups (p=0.493) although, there were a higher proportion of patients on the IFU with type2 and 3 IF compared to non-IFU wards, 63% versus 10%.

Table 4.13 Demographics of patients with catheter related sepsis

	Pre-IFU	**Post IFU 2010/2011**		**P value**
	2009/2010	*IFU*	*Non-IFU*	
N	29	8	10	
Age (median in years (IQR))	65 (53-76)	58 (46-68)	74 (62-80)	0.734†
Gender (male:female)	19:10	4:4	6:4	0.495‡
Length of stay (median in days (IQR))	40 (29-91)	47 (23-67)	30 (18-81)	0.303†
ITU admission (%)	15 (52)	2 (25)	2 (20)	0.068§
Type of IF (%)				0.493
1	22 (76)	3 (38)	9 (90)	
2	6 (21)	4 (50)	-	
3	1 (3)	1 (13)	1 (10)	

‡ Chi-Square, †Mann Whitney U, § Fisher's exact

There was a statistically significant reduction in the rates of CRS from 10.01 per 1000 PN days pre-IFU compared to 4.49 per 1000 PN days post-IFU (p<0.006) (table 4.14). There was a small difference in the rates of infection between IFU and non-IFU wards, 3.64 per 1000 PN days and 5.52 per 1000 PN days, although this did not reach statistical significance (p=0.374). Despite the increased proportions of patients with type 2 and 3 IF treated on the IFU there was no difference in the median number of days of PN per patient between these two groups (p=0.142).

Table 4.14 Incidence of catheter related sepsis

	Pre-IFU	**Post IFU 2010/2011**		**P value**
	2009/2010	***IFU***	***Non-IFU***	
N	29	8	10	
Number of infections	29	8	10	
Total days of PN	2897	2198	1811	
Median number of days per patient	12 (8-24)	15 (9-41)	8 (5-23)	0.742†
Rate of infection (per 1000 PN days)	10.01	3.64	5.52	<0.006¥

¥ Z test, † Mann Whitney

There were no differences between the patients with regard to nutritional status between the pre and post-IFU groups (see table 4.15). There were also no differences with respect to the proportion of patients who had not undergone surgery 9 (31%) pre-IFU and 5(28%) post-IFU (p=0.586).

Table 4.15 Nutritional indices of patients with catheter related sepsis

	Pre-IFU	IFU	Non-IFU	Total	p value
N	29	8	10	47	
BMI (median (IQR))	23 (20-30)	24 (21-29)	23 (17-28)	23 (20-29)	0.405†
% weight loss (median (IQR))	5 (0-20)	7 (5-16)	7 (0-13)	5 (0-17)	0.051†
Days no nutrition (median (IQR))	0 (0-7)	7 (0-18)	6 (2-7)	2 (0-8)	0.619†
MUST score	2 (2-4)	4 (2-4)	3 (2-6)	3 (2-4)	0.904†

†Mann Whitney U

4.3.2.3 Extended data collection 2011-2012

Due to the relatively small number of patients who developed CRS per year and an early suggestion of improvements in patients treated on the IFU a further year of data (6th April 2011-5th April 2012) were subsequently analysed to try and establish any differences between catheter types, causative organisms and adherence to investigative protocols.

The overall rate of infection for combined IFU and non-IFU wards is largely unchanged between 2010-2011 (4.49 episodes per 1000 PN days) and 2011-2012 (4.44 per 1000 PN days) (table 4.16). However, in 2011-2012 there was a statistical difference between infection rates on the IFU (1.80 per 1000 PN days) and those on non-IFU wards (8.21 per 1000 PN days, $p<0.0001$). There incidence of infection on non-IFU wards in 20011-12 was similar to the historical rate of CRS (2009-2010, $p=0.322$).

Table 4.16 Incidence of catheter related sepsis 2010-2012

	Post IFU 2010/2011		Post IFU 2011-2012	
	IFU	**Non-IFU**	**IFU**	**Non-IFU**
Number of infections	8	10	5	16
Total days of PN	2198	1811	2778	1950
Rate of infection (per 1000 PN days)	3.64	5.52	1.80	8.21

4.3.2.4 Type of catheter

For all infections the type of catheter that became infected was recorded (see table 4.17). Data were not accurately recorded to indicate the number of PN days per catheter and were further limited by the fact that many patients had more than one catheter or type of catheter during their PN treatment. However, for a subset of patients treated across all areas between 2009-2011 that had only 1 episode of PN with one catheter data were available. 245 had a temporary CVC, of which 30 (12.2%) subsequently developed evidence of CRS. This compares to 179 patients who had a PICC, of which only 11 (6.5%) developed CRS. Therefore in this sub-group of patients there was an increase in CRS in those treated with temporary CVCs compared to PICCs (P = 0.0451). However this did not take into account the duration of treatment.

4.3.2.5 Investigation of catheter related sepsis

The minimum requirement for appropriate investigation of suspected CRS in all patients was defined as paired peripheral and central catheter cultures and was detailed in the protocol. Where only a single culture was obtained this was also recorded. The proportion of patients diagnosed with CRS who met this criteria between IFU and non-IFU wards in 2010-2012, 100% versus 69% (p=0.035)(table 4.17). The increased rate of appropriate investigation led to an increase in the categorisation of catheter sepsis by the highest order of microbiological proof (CRBSI) from 38% to 72% in the 2 years since the IFU opened. There was a difference between

IFU and non-IFU wards with regard to ability categorise infections to CRBSI 85% versus 65%. Of the patients with catheter suspected blood stream infections (CSBSI), the lowest microbiological proof of infection, only 27% of patients underwent minimum levels of investigation, compared to 39% and 100% in catheter associated blood stream infections (CASBI) and CRBSI respectively.

Table 4.17 Types of catheters and investigations undertaken in patients with CRS

	Pre-IFU 2009-2010	**Post IFU 2010-2012**		**Total**
		IFU	**Non-IFU**	
N	*29*	13	26	68
Device (%)				
CVC	*17 (59)*	7 (54)	17 (65)	41 (60)
PICC	*9 (31)*	5 (39)	7 (27)	21 (31)
Tunnelled CVC	*3 (10)*	1 (8)	1 (4)	5 (7)
Port	*0 (0)*	(0)	1 (4)	1 (1)
Microbiological Investigations				
Paired cultures (%)	*15 (52)*	13 (100)	18 (69)	46 (68)
Single blood culture (%)	*14 (48)*	0 (0)	8 (31)	22 (32)
Type of Infection				
CRBSI (%)	*11 (38)*	11 (85)	17 (65)	39 (57)
CABSI (%)	*11 (38)*	2 (15)	5 (19)	18 (26)
CSBSI (%)	*7 (24)*	0 (0)	4 (15)	11 (16)

This table illustrates the number of patients with CRS classified by the clinical area in which an episode of CRS occurred, the types of catheter which were infected, the extent of culture investigations and classification of CRS by levels of microbiological proof.

The commonest causative organisms were coagulase negative staphylococcus, responsible for 59% of infections, although this proportion is higher on the IFU where improved rates of investigation were identified (table 4.18). Other gram-positive infections included staphylococcus

aureus, Enterococcus and clostridium species. Overall gram-negative infections made up a small proportion of infections and were caused by pseudomonas, E coli and stenotrophomonas. 78% of those culture negative infections occurred prior to the IFU.

Table 4.18 Causative organisms

	2009-2010 Pre-IFU	Post-IFU 2010-2012		Total
		IFU	Post IFU	
N	29	13	26	68
Coagulase negative Staphylococcus (%)	13 (45)	10 (77)	17 (65)	40 (59)
Other Gram positive organisms (%)	5 (17)	2 (15)	4 (15)	11 (16)
Gram negative organisms (%)	3 (10)	-	1 (4)	4 (6)
Fungal (%)	1 (3)	1 (8)	2 (8)	4 (6)
No Growth (%)	7 (24)	-	2 (8)	9 (13)

As a direct consequence of CRS 4 (6%) patients were admitted to ITU for a total of 11 days. There were no deaths attributable to CRS. Rates of successful antibiotic treatment and catheter salvage were not assessed as most patients had temporary vascular access and on most occasions the catheter was removed as part of treatment.

4.3.3 Discussion

This study has a number of limitations including its observational nature and a lack of specific data regarding catheter details. Nonetheless it is reflects actual clinical practice and demonstrates that relatively simple measures can result in significant improvements in clinical outcomes. Additionally it serves to illustrate the large numbers of patients required to demonstrate reductions in relatively infrequent complications and the challenges posed in accurate recording of catheter related details in clinical practice.

There were few differences between those who developed CRS and those who did not with respect to age, emergency admission, nutritional status, PN indication, admission category and the number who required an ITU admission. However, patients who developed CRS had a significantly longer length of stay 38 versus 26 days ($p<0.001$). This study was not designed to specifically assess outcomes of those who developed CRS and doubtless there are other factors which contributed to this finding, however this is potentially significant and this observation would merit further assessment.

In the broad measures described above there were no significant differences between patients with and without CRS. However there were differences with regard to the patients admitted onto the IFU. There were two potential reasons why patients were not able to transfer to the IFU; greater requirement for condition specific specialist nursing in another department or the IFU had reached capacity. Therefore many of the patients not transferred were unwell in critical care environments, surgical high dependency, cardiac high dependency, or haemato-oncology isolation beds. Typically in these clinical areas nursing ratios would be higher than the IFU with a perception of greater experience in central catheter access techniques. However, it is not possible in this type of study to take into account these potential confounding factors of clinical need and nursing skill mix.

These data not only demonstrate a reduction in CRS from Pre IFU rates of 10.01 to 4.44 episodes per 1000 ($p=0.004$) but during the evolution of the IFU differences were identified between the IFU and non-IFU wards , albeit that they did not become statistically significant until 2011-2012. This time lag was most likely due to the IFU opening 'live' without specific additional nurse resource or training beforehand, indicating that there was a significant staff education and training affect that occurred during the initial few months. The aim of every unit should be to have no episodes of CRS. In reality it will always remain an issue in IF practice. Pronovost et al reported a median rate of CRS of 0 per 1000 catheter days at 18 months however, this was in a different population using different interventions and definitions (135). There are no guidelines regarding an acceptable incidence of CRS but setting standards for IF units at a national level will result in improvements as has been the case for other healthcare acquired infections.

In many respects it is perhaps surprising that there were not more infections seen in the IFU compared to non-IFU wards. An IFU cohorts sick patients into a single ward who were previously dispersed throughout the hospital, they require multiple time consuming aseptic connections of PN and other drugs along with other intensive nursing care. The IFU in this institution had no significant changes in nursing to patient ratios. Therefore it is easy to imagine how when

pressured by time standards of PN care could have declined. When this workload is taken into consideration it is surprising that the improvements in CRS were so marked.

Pronovost et al demonstrated that implementing a patient safety initiative based on catheter insertion technique accompanied by increased awareness and cultural change significantly reduced CRS (135). In this study there were no changes with regard to clinical practice but, there was a major focus on staff education and training with regard to adherence to existing catheter access techniques. Although this was not a controlled study it does appear to demonstrate the positive effect of education and training and like Pronovost et al, the importance of cultural change.

The results also show that the proportion of patients with CRS who underwent the minimum level of investigation was higher in those on the IFU 100% versus 69% on non-IFU wards (p=0.035). This enables an increase in the ability to accurately diagnose infections with a higher degree of microbiological certainty, minimises investigations for alternative sources of sepsis e.g. CT scanning and allows for more targeted antimicrobial therapy. A further study to assess the proportion of patients with suspected sepsis whilst on PN who do not have CRS that undergo appropriate investigation is needed to investigate these assumptions.

The causative micro-organisms in CRS were broadly similar on IFU and non-IFU wards with coagulase negative staphylococcus aureus accounting for 69% of infections. The high prevalence of this common skin commensal would suggest that introduction of infection at the hub is the most common mechanism of infection. The number of non-gram positive infections are too small to compare statistically but appear broadly similar. However the causative organisms in the pre-IFU group appear very different, predominantly due to a high proportion of cases which were culture negative, which as previously described likely arises for a lack of appropriate investigation.

These data also provide some limited evidence that temporary CVCs are potentially at higher risk of CRS than receiving PN via PICCs, 12.2% versus 6.5%. Data from this study were unable, however, to report infection rates per PN or catheter day which would make a more valid comparison. There were also many uncontrolled factors that were not recorded including variation in insertion techniques and catheter management on the ward. Nevertheless, these are potentially useful observations which could be formerly assessed in a future prospective study.

In acute IF the vast majority of patients have type 1 IF and are likely to receive PN via temporary CVCs or PICC s. Therefore, in the majority of patients it will be appropriate to remove infected catheters as part of the management of CRS. A few patients may have longer term tunnelled catheters inserted or have complex intravenous access issues whereby attempts are made at

catheter salvage. There are no universally standardised protocols for this treatment and the number of affected patients with acute IF are likely to be very small. Salvaging catheters often involves alternatives to central venous access and therefore withholding PN for periods of up to 2 weeks, which in acutely unwell patients is often impractical. This perhaps explains why there is limited published data regarding CRS eradication rates in acute IF as opposed to HPN patients.

In conclusion, the results of this study appear to demonstrate that managing patients with IF in a dedicated unit results in improvements in CRS. This is predominantly thought to be the result of a cultural change and training within the unit rather than changes to clinical practice. These improvements are broadly similar to those identified in other quality improvement studies but also share the limitations of drawing conclusions from practice based change.

4.4 Chapter summary

Data from the NCEPOD study highlighted significant variability and concerns with respect to the quality of PN related patient care in UK hospitals. However, due to the nature of the study and subject matter much of the report was based on expert opinion and not on adherence to strict guidelines. It is therefore difficult to collect directly comparable data and indeed the studies described here have demonstrated that specific objective measurement of standards of PN care in hospitalised patients with IF is difficult and time consuming.

Despite the reservations expressed above, this series of studies suggests that in this IF centre standards of PN care are generally good compared to results from the NCEPOD study particularly in the areas of clinical assessment, indication, decision making, identifying patients at high risk of refeeding syndrome and appropriate prescribing. This largely reflects the training and experience of the nutrition support team in initiating PN.

The areas where care could be improved were those outside of the immediate control of the NST, such as biochemical monitoring and aspects of catheter care. These are areas which now they have been highlighted will be improved upon, especially with a dedicated IFU potentially facilitating improved communication between clinical teams.

These studies have also demonstrated clear benefits of dedicated intestinal failure units. CRS rates are arguably one of the most important objective markers of acute IF care. This study has shown that through training and cultural change without any other intervention rates of infection can be significantly improved. PN administration and recording is also an important component of care in patients with IF and this study has demonstrated numerically significant differences

between the IFU and non-IFU wards, whether this translates into meaningful clinical differences, however would be challenging to demonstrate.

Overall these studies support the hypothesis that standards of PN care in IF centres are higher than seen nationally and real life data appear to support the improvements that have resulted from developing a dedicated IFU. However these are uncontrolled clinical studies from a single centre, with many potential confounding factors that prevent widespread generalisation. Therefore it would be presumptive to state that this is a model which should be universally adopted, even though it seems a logical progression, particularly as the development of dedicated units in other specialities has resulted in significant improvements to patient outcomes, as previously discussed. In addition to supporting practice change internally, these data suggest further consideration should be given as to how quality indicators can be collected nationally to ensure other hospitals are providing good standards of care and make improvements for the future.

Chapter 5: Identifying patients with type 2 intestinal failure

The literature review demonstrated that there are significant knowledge gaps regarding incidence, aetiology, patient outcomes and levels of IF activity. Whilst the classification proposed by Pironi et al provides a framework for characterising IF, in practice these definitions still require significant interpretation by individual clinicians and does not enable patients to be easily identified (4).

In clinical practice there are two main limitations of the existing IF sub classification; awareness of the existence of a definition and the need for interpretation. These are potentially significant barriers to clinicians who have very infrequent exposure to cases. Interpretation of the sub classification in the context of managing complex critically unwell patients can be difficult, potentially leading to reduced recognition that an individual has developed established type 2 or 3 IF. A screening tool which is easy for non-specialists to use would potentially have clinical utility, enabling earlier discussions with specialist centres. A screening tool or criteria for identifying type 2 or 3 IF may also empower nutrition support teams to facilitate discussions with clinicians less familiar with the principles of IF management.

A surrogate definition of type 2 IF used by some authorities is 'patients who have received more than 28 days of PN' but there is no evidence to support this approach. This study was therefore designed to examine whether the number of days a patient receives PN can act as a useful screening or even diagnostic tool in identifying type 2 IF.

Due to the existing descriptive definition, similar issues exist in clinical practice with regard to identifying what constitutes a patient with type 2 IF, what is intestinal failure surgery and which patients benefit from management in specialist units. As reported in the literature review, it is anticipated that the overall number of patients and procedures performed in type 2 IF are small but without clearly identifying what constitutes this type of patient and operation it is impossible to determine clinical activity or plan services. Being able to easily identify type 2 IF and an IF surgical operation in clinical practice is very important in terms of improving outcomes and ensuring appropriate tariffs for complex admissions and procedures. These four areas; definition, patient outcomes, service provision and tariffs are very closely interlinked.

The second component of this study was to apply the proposed criteria for IF surgery to a cohort of patients who fulfilled the descriptive definition for type 2 IF proposed by Lal (3). This was considered in terms of the utility in clinical practice and how this could be used to further benchmarking, audit, tariffs and research.

5.1 Methodology

5.1.1 Patient selection

Two separate searches of the NST database over a three year period from January 2008 to December 2010 were undertaken. The first search identified all patients who were registered on the NST database as having been diagnosed with type 2 intestinal failure. The second search identified all patients who required more than 28 days of parenteral nutrition during a single hospital admission.

The clinical records of each case identified from both searches were subsequently reviewed by three clinicians experienced in the management of IF. Each case was assessed using the definitions proposed by Lal to categorise into IF subtype (3). Any differences in opinion between clinicians were discussed until a final conclusion was reached, this was considered as the 'gold standard' for the purposes of further analysis in the absence of additional assessment techniques being available. All cases of type 2 IF were subsequently sub-classified by the same three clinicians according to nationally proposed IF surgery criteria (see table 2.2).

5.2 Results

5.2.1 Duration of parenteral nutrition treatment

There were a total of 692 patients treated with PN in this time period. The two combined search criteria identified a total of 74 patients who had received more than 28 days of PN or were managed as type 2 IF.

There were 45 patients with type 2 IF, of which 41 had received more than 28 days of PN either in this institution or the referring hospital. Nutritional requirements in the other 4 patients with type 2 IF were met through a combination of shorter duration PN and/or enteral tube feeding and/or oral nutritional supplements There were a total of 29 patients who had received more than 28 days of PN who had non-type 2 IF (type 1 IF or type 3 IF). These data were then used to identify sensitivities and specificities of the 28 day criteria to diagnose type 2 IF (figure 5.1).

	Patients with type 2 IF		
	Type 2 IF	Non-type 2 IF	
>28 days of PN	41 *True positive*	29 *False positive*	Positive predictive value = 59%
<28 days of PN or less	4 *False negative*	618 *True Negative*	Negative predictive value = 99%
	Sensitivity = 91%	Specificity = 96%	

False positive rate= 4%, False negative rate = 9%

Figure 5.1 Sensitivities and specificities of PN duration greater than 28 days

Further analysis was subsequently undertaken to characterise any differences there may have been between patients who had type 2 IF and those who required prolonged courses of parenteral nutrition (table 5.1).

Table 5.1 Characteristics of patients with type 2 IF and non-type 2 IF

	Type 2 IF	**Non-type 2 IF**	**p value**
N	45	29	
Age (median (IQR))	59 (49-69)	60 (44-68)	0.678†
Male (%)	24 (53)	15 (52)	0.892‡
Must score (median (IQR))	3 (2-4)	4 (2-5)	0.186†
Laparostomy (%)	15 (33)	0 (0)	0.000‡
Number of operations (median (IQR))	2 (1-3)	1 (0-1)	0.001†
Days on ITU (median (IQR))	2 (0-13)	0 (0-2)	0.011†
Days of TPN (median (IQR))	53 (33-89)	44 (33-58)	0.124†
Length of stay (days) (median ((IQR))	99 (65-134)	65 (55-80)	0.004†

‡Chi Square †Mann-Whitney U Test

Of the 74 patients with either type 2 IF or the need for more than 28 days of PN there were, 21 patients with type 1 IF, 45 patients with type 2 IF and 8 patients with type 3 IF. In all of the cases identified as type 3 IF the prolonged duration of PN related to an admission for assessment and set up for HPN. There was no statistical difference with regard to median age, gender or median MUST score between the patients with type 2 IF and non-type type 2 IF, 59 versus 60 (p=0.678), 53% versus 52% (p=0.892) and 3 versus 4 (p=0.186) respectively.

At the point of initial assessment by the NST the median number of operations in the type 2 IF group was 2 (interquartile range 1-3). This was fewer than anticipated however, it was significantly greater than that of the non-type 2 IF patients, median 1 (interquartile range 0-1) (p=0.001).

Patients with type 2 IF had a greater length of stay in ITU 2 days (IQR 0-13) compared to non-type 2 IF 0 days (IQR 0-2) (p=0.011). Patients with type 2 IF also had a significantly longer length of stay, 99 days (IQR 65-134) versus 65 (55-80) (p=0.004). There was also a higher proportion of patients with a laparostomy 33% versus 0% (p<0.001) in patients with type 2 IF.

There were no significant differences in the total number of PN days between patients with type 2IF and non-type 2 IF, 53 days (IQR 33-89) versus 44(IQR 33-58) (p=0.124). Following the exclusion of patients with type 3 IF, resulting in a group with 'prolonged' type 1 IF, there was still no significant difference between this group and those with type 2 IF with respect to the duration of PN treatment, 53 days (interquartile range 33-89) versus 38 (33-62) (p=0.135). Furthermore, exclusion of 'prolonged' type 1 IF patients who did not undergo surgery also failed to demonstrate a difference in duration of PN treatment, type 2 53 days (IQR 33-89) versus non-type 2 patients median 38 (IQR 33-65) (p=0.177).

5.2.2 Intestinal failure surgery criteria

Of the patients with type 1 or type 3 IF who had received more than 28 days of PN , none met any of the IF surgery criteria. As described in 5.2.1, 4 patients with type 2 IF did not receive 28 days of PN treatment, yet all fulfilled at least one of the IF surgery criteria. 43 patients out of the 45 who met the descriptive definition for type 2 IF met one or more IF surgery criteria (table 2.2). The two patients with type 2 IF who failed to meet the IF surgery criteria were;

Patient A: A 71 year old male admitted with acute severe gallstone pancreatitis. He underwent a pancreatic necrosectomy and post –operatively developed intra-abdominal collections which initially required further laparotomies and subsequent radiologically guided abdominal drainage. He was unable to tolerate enteral (jejunal) feeding due to protracted ileus. The patient had an 11 day ITU stay, required 51 days of PN and a total length of stay of 70 days.

It was considered that this patient did not fulfil the IF surgery criteria as there was no evidence of an ECF or a particularly 'hostile abdomen' and no other surgery was indicated. Although the patient fulfilled the definition for type 2 IF with intraabdominal sepsis, metabolic instability with vascular access complications.

Patient B: A 56 year old female patient with previous extensive small bowel resections for Crohn's disease and adhesions, resulting in 100 cm of jejunum anastomosed to ascending colon in continuity. She was significantly malnourished prior to admission. She presented with small bowel obstruction secondary to a long Crohn's stricture 50cm from the DJ flexure and rapidly developed an aspiration pneumonia complicated by adult respiratory distress syndrome, requiring

ITU admission and ventilation. She was considered too unwell for emergency surgery in the short term due to chest sepsis and subsequent post critical care polymyopathy combined with malnutrition. ITU stay 13 days, PN days 171 total hospital stay 221. She did not have a focus of intra-abdominal sepsis requiring surgery or radiological drainage. She was managed with PN and a venting percutaneous gastrostomy. She was discharged on HPN and planned for subsequent surgical resection when clinically stable.

It was felt on review that this patient fulfilled the criteria for type 2 IF with complex nutritional issues and periods of metabolic instability but was never well enough in hospital to undergo abdominal surgery.

After the IF surgery criteria were applied to the cohort of patients who had received more than 28 days of PN or were considered to have type 2 IF sensitivities and specificities were calculated to evaluate the accuracy of these criteria (figure 5.2). This demonstrated that in this population these criteria have a positive predictive value of 100% for identifying IF surgery in this cohort of patients and 100% specificity. Therefore these criteria are potentially useful in clinical practice for recording clinical activity and patient outcomes.

	Type 2 IF	Non-type 2 IF	
IF surgery criteria	43 *True positive*	0 *False positive*	Positive predictive value = 100%
Not IF surgery criteria	2 *False negative*	29 *True negative*	Negative predictive value =94 %
	Sensitivity = 96%	Specificity = 100%	

Figure 5.2 Sensitivities and specificities of IF surgery criteria

5.3 Discussion

These data demonstrate that labelling all patients who had received more than 28 days of PN as having type 2 IF is inaccurate in nearly 50% of cases and hence this criterion, taken in isolation is not a useful diagnostic test. There was no significant difference in duration of PN in the type 2 IF group than non-type 2 IF (median 53 days versus 44 days p=0.124). This is perhaps unsurprising considering the number of circumstances in which prolonged PN may be indicated. Even allowing for patients with type 3 IF and those with type 1 IF who did not undergo abdominal surgery this simple classification based solely on the duration of PN failed to differentiate patients with type 2 IF.

Although receiving more than 28 days of PN does not appear to be a useful test for diagnosing type 2 IF, it could still be a useful criterion for screening patients in whom further consideration of the diagnosis should be given. When this was applied to all patients treated in this unit over a 3 year period it had a high sensitivity of 91%, meaning few cases of type 2 IF were missed. It also had a high specificity (96%), therefore identifying only a relatively small number of false positives.

When the IF surgery criteria were applied to the population of patients identified as having type 2 IF or those who had received more than 28 days of PN, 96% of all the cases of type 2 IF were identified, yielding a positive predictive value of 100%. Therefore, as anticipated, this suggests these criteria are extremely good at identifying type 2 IF. This is an important finding as these criteria had never been previously validated.

These results therefore indicate the potential use of more than 28 days of PN as a screening test for type 2 IF and the IF surgery criteria as definable objective descriptions for data reporting. A clinical model can then be proposed whereby all patients who receive more than 28 days of PN at any hospital should be discussed with a specialist IF centre for advice regarding further management. This would help develop a more proactive strategy to managing complex patients, potentially preventing progression to the more complex end of the IF spectrum with potential benefits in reductions in morbidity, mortality and cost. Furthermore, it should be straightforward to identify the number of patients treated with 28 days of PN or more in every UK hospital with national reporting to assess levels of clinical activity and subsequent referral patterns to specialist centres.

The IF surgery criteria have a high sensitivity and specificity in identifying patients with type 2 IF when applied to this population. Were these to become recognised and adopted at a national level they could therefore be used to report clinical activity and outcomes. This would then help to improve the quality of care and enable comparisons to be made between IF centres, even

allowing for differences in case mix. It would also help the planning of national IF service provision. However, the main utility maybe the use of these criteria as clinical codes for 'IF tariffs' in designated IF centres to enable the development of a sustainable funding mechanism. This will be discussed further in chapter 7.

If in a larger study the IF surgery criteria were confirmed to miss only a very small percentage of patients who meet the current definition proposed by Lal for type 2IF, it could be argued that the IF surgery criteria should be used exclusively to define type 2 IF (3). The rationale being that these criteria are likely to be more clinically relevant and could harmonise interpretation and data collection nationally and internationally.

This study has a number of limitations, being both retrospective and reliant on the accuracy of information coded in the database. In addition there was insufficient time for all three clinicians to retrospectively review the notes of all 692 patients with regard to applying the IF surgery criteria to determine if any additional cases of type2 IF surgery could be identified that had previously been incorrectly coded. Nevertheless, it was felt unlikely that such an exercise would have yielded a significant number of additional patients.

Another limitation is that the population in this study is not generalisable to other hospitals due to an atypical case mix of existing type 2 and 3 IF patients alongside patients included from an extended range of specialist hepatobiliary, oesophagogastric, cardiothoracic and haematoncology services. Patients undergoing more extensive and complex surgery would logically be expected to have more complications and require prolonged periods of PN support.

The nature of the background population influences the reported sensitivity and specificity of these data. However by reviewing the cases individually it enabled a clinical assessment of the validity of the two criteria in categorising patients with type 2 IF and prolonged PN requirements. A logical extension to this work would be to expand the study population to include local secondary care hospitals and other tertiary IF units, with the addition of external assessors. As well as increasing the size of the study population, it would be make the results more applicable at a national level.

Whilst this proposed model of identifying type 2 IF is attractive due to the simplicity of PN duration as a screening tool and the proposed IF surgical criteria being a more practical and clinically relevant definition of type 2 IF, there are a number of drawbacks. As in this study, there will always be a small number of patients who fulfil the definition of type 2 IF but not the surgical criteria. However, if these numbers are small then this maybe an acceptable trade-off for clinical utility.

In addition, this model does not provide a solution to the specialist service provision for patients who may benefit from being treated in IF centres due to specific PN complications or whose PN duration is causing concern yet do not meet criteria for type 2 IF. These are an important group of patients to consider when planning a national IF infrastructure but there are currently even less data regarding aetiology, incidence or outcome which to base these plans on.

Despite the limitations of the study, real life data have demonstrated that using duration of PN treatment for more than 28 days is not a diagnostic criterion for type 2 IF. Similarly, the IF surgery classification has been shown to be valid and clinically relevant. In this cohort there was good correlation with the type 2 IF definition proposed by Lal and may be a practical next step for defining type 2 IF in clinical practice. A model utilising both these criteria is likely to facilitate the identification of patients whom additional early specialist input is likely to be beneficial. These results are highly relevant to current issues regarding IF service provision and funding.

Chapter 6: Clinical outcomes in patients with type 2 intestinal failure

Identification of outcome measures and standards is an important step when trying to establish evidence for the need and effectiveness of specialist IF centres. Unfortunately, however, due to the historical lack of a consensus definition for IF sub classification, there is a paucity of published literature characterising type 2 IF patients and their outcomes. There is also little published on the aspects of clinical care which could be considered good indicators of quality, although national expert bodies have suggested possible criteria.

This study was designed to assess the demographics, aetiology, IF surgery classification, outcomes and complications in patients with type 2 IF managed in a regional specialist unit. These data were then considered in relation to identifying potential quality indicators.

6.1 Methodology

6.1.1 Case selection

Clinical information was collected both prospectively and retrospectively from the electronic and paper records of all consecutive adult patients with type 2 IF managed by the regional intestinal failure team at University Hospital Southampton NHS Foundation Trust over a 30 month period, from 1st January 2010 to the 30th June 2012. Patients were included in the study if they had been discharged after an admission for assessment and stabilisation even if they had not completed their planned treatment in the form of definitive reconstructive surgery.

6.1.2 Data collection

Data collected included gender, age at referral, aetiology, mechanism of intestinal failure, and nutritional status. All patients were classified according to the IF surgery criteria (table 2.2). In those who were yet to complete treatment, managed conservatively (non-operative) or had died this classification was also applied but it was noted that they had not undergone surgery. Patients were also classified to reflect the type of admission based on whether this was an index admission, the patients first admission for assessment and stabilisation or a planned admission for definitive reconstructive surgery.

6.1.3 General type 2 intestinal failure management

All patients were managed by the 'SNAP' principles described in section 2.3.2. In accordance with the available evidence previously described, reconstructive surgery was delayed to allow time for resolution of dense adhesions and importantly the opportunity for the patient to recover physical and psychological reserves. Therefore in this series a significant proportion of patients were discharged home after the index admission and readmitted electively for definitive surgery some months later. However, this was not necessary in all cases.

6.1.4 Surgical intestinal failure management

Reconstructive surgery for enterocutaneous fistulae consisted of laparotomy, adhesionolysis and en bloc resection of involved bowel and overlying skin with hand sewn anastomosis. None of the fistulae were oversewn and there were no stapled anastomoses. Abdominal wall closure was undertaken using component separation techniques and where necessary insertion of biologic mesh (Strattice™). Surgery for restoration of intestinal continuity was also performed with a laparotomy, adhesionolyisis and hand sewn anastomosis.

6.1.5 Outcome measures

During an index admission data were recorded for septic complications at presentation, complications of PN, length of stay and mortality. In patients who had undergone reconstructive surgery, operative duration, relaparotomy rates, readmission to critical care and mortality were also recorded. Additional data were collected regarding the proportion of patients who were nutritionally autonomous on completion of treatment, recurrence of fistulation and mortality.

6.2 Results

6.2.1 Demographics and aetiology

During the 30 month time period 48 patients were managed by the IF service. The mean age at first presentation to this service was 52 years (standard deviation 18 years), with a range of 18-85 years. There were 23 males (48%) and 25 females (52%). There were 14 referring hospitals, regional referrals resulting in 60% of the case load.

The most frequent cause of type 2 IF resulted from complications following surgery 29 patients (60%), Crohn's disease 8 patients (17%), mesenteric ischaemia 7 patients (15%), malrotation 2 patients (4%), trauma 1 patient (2%) and delayed radiotherapy complications 1 patient (2%). In

patients who had developed complications following surgery the original indication is listed in Table 6.1.

The operative complications that precipitated IF occurred as a result of fistulation and sepsis in 24 of the 29 subjects (83%). Of the eight patients with Crohn's disease, 5 patients developed IF as a result of sepsis and spontaneous fistulation as part of their disease process. Three Crohn's patients developed abdominal sepsis following surgery. All patients with ischaemia and malrotation had complications from abdominal sepsis. The median number of laparotomies relating to the acute problems prior to referral to the IF team was 3 (interquartile range 2-4), with 6 patients having had 5 or more.

Table 6.1 Indications for original surgery

Emergency surgery	**Elective surgery**
Small bowel obstruction (small bowel resection) 4 adhesions 3 secondary to radiotherapy 1 Parastomal hernia	2 Reversal of Hartmann's procedure
	2 Closure of defunctioning ileostomy
	Rectal cancer (abdominoperineal resection)
	Radiation enteritis (defunctioning ileostomy)
2 Diverticular perforations (Hartmann's procedure)	Neuroendocrine tumour (sub-total enterectomy)
	Chronic pancreatitis (Berger's procedure)
Caecal volvulus (right hemicolectomy)	Gastric cancer (Roux-en-Y)
Ulcerative colitis (sub-total colectomy)	Bariatric surgery (Roux-en-Y)
Acute pancreatitis (necrosectomy)	Exploratory laparotomy for abdominal pain
Appendicitis (appendicectomy)	Chronic pseudobstruction (defunctioning ileostomy)
Spontaneous perforation colon cancer (right hemicolectomy)	2 Gynaecological surgery for endometriosis and pelvic pain

All patients were classified by the IF surgery criteria or the category that best represented those awaiting reconstructive surgery or who did not require surgical intervention (Table 6.2).

Table 6.2 IF surgery category

	Reconstructive surgery	**Awaiting surgery or non-surgical intervention**	**Total (%)**
Enteric fistulation associated with laparostomy	11	2 awaiting surgery 1 conservative management	14 (29)
Enteric fistulation associated with other organs	3	2 conservative management	5 (10)
Enteric fistulation associated with abdominal sepsis requiring radiological or surgical drainage	4	1 Awaiting surgery 2 radiological drainage only (1 death)	7 (15)
Recurrent enteric fistulation following previous attempts at repair	1		1 (2)
Hostile abdomen associated with re-operation for adhesions	3		3 (6)
Hostile abdomen associated with abdominal sepsis requiring surgical drainage	2		2 (4)
Hostile abdomen associated with radiation enteritis	1		1 (2)
Abdominal surgery where planned operative intervention would deliberately result in a period of intestinal failure		1 (death)	1 (2)
Abdominal surgery where the primary aim of surgery is to restore intestinal continuity allowing cessation of parenteral nutrition	11	2 awaiting surgery	13 (27)
Abdominal surgery requiring complex abdominal wall reconstruction	1		1 (2)

6.2.2 Index admissions

Due to the diversity of the patient cohort and the relatively small number of subjects further characterisation of the index admission was based on the unifying SNAP approach to management.

There were 44 index admissions, acute admissions for assessment and stabilisation. 12 (27.3%) patients underwent reconstructive surgery during the index admission. 26 (59.0%) patients were discharged with reconstructive surgery planned at a later stage. 3 (6.8%) patients were discharged with low volume fistulas and managed conservatively due to the risks of further surgery outweighing potential benefits, predominantly as a result of physical frailty. One (2.3%) patient was treated with repeated radiological drainage as definitive treatment and subsequently discharged without the need for further operative intervention. There were 2 deaths (4.5%).

The median length of stay of the index admission was 76 days (interquartile range 52-123) with a median ITU stay of 0 days (interquartile range 0-7).

6.2.2.1 Sepsis

In those patients transferred acutely from other hospitals 21 of 26 (81%) had evidence of on-going sepsis, median admission CRP 109 mg/L (interquartile range 36-220 mg/L) albumin 23 g/L (interquartile range 18-27 g/L). This included 2 patients with active but previously undiagnosed CRS. 15 of the 19 patients with abdominal sepsis had radiological evidence of one or more intra-abdominal collections on their first CT and required radiological drainage within 72 hours of admission. There were 5 laparotomies undertaken for sepsis which was not controlled despite antimicrobial therapy with or without radiological drainage. There were no deaths related to these procedures.

6.2.2.2 Nutritional assessment

At initial assessment on the index admission the median BMI was 22 kg/m^2 (interquartile range 19-28), median percentage weight loss 11% (interquartile range 3-19) and median MUST score 2 (interquartile range 2-4). One patient was excluded from this analysis as he had just turned 16 years of age and as a consequence of longstanding Crohn's disease had significant growth arrest and pubertal delay. Regional patients had a lower median BMI 21 kg/m^2 (IQR 17-26) compared to local patients 24 (IQR 20-33) although this just fell short of statistical significance (p=0.055). The median percentage weight loss was significantly greater in patients referred from other hospitals 15% (IQR 9-25) compared to 7% (IQR 0-12) (p=0.007). There was no difference in predicted MUST scores between the groups (table 6.3).

Table 6.3 Nutritional assessment

	Local	**Regional**	**Total**	**p value**
N	18	25	43	
BMI (kg/m^2) (median (IQR))	24 (20-33)	21 (17-26)	22 (19-28)	0.055§
% Weight loss (median (IQR))	7 (0-12)	15 (9-25)	11 (3-19)	0.007§
MUST (median (IQR))	2 (2-3)	3 (2-4)	2 (2-4)	0.186§

§Mann-Whitney U IQR inter quartile range

Analysis was undertaken to determine if nutritional status had an association with other patient characteristics such as emergency or elective surgery and number of laparotomies previously undertaken. Analysis was also undertaken to assess if nutritional status affected length of stay, requirement for ITU or number of days from last to definitive surgery (table 6.4 and table 6.5).

Table 6.4 Patient characteristics grouped by body mass index

	Body Mass Index (kg/m^2)		Total	p value
	BMI ≤ 20	**BMI>20**		
Number	16	27	43	
Age (years) (mean (sd))	50 (23)	57 (14)	54 (18)	0.250†
Elective surgery (%)	5 (31)	9 (33)	14 (33)	0.888‡
Length of stay (days) (median (IQR))	93 (56-110)	90 (52-151)	90 (56-123)	0.599§
ITU stay (days) (median (IQR))	0 (0-0)	2 (0-13)	0 (0-7)	0.028§
Number of laparotomies (median (IQR))	1 (1-4)	2 (2-4)	3 (2-4)	0.644§
Laparostomy (%)	4 (25)	11 (41)	15 (35)	0.295‡
Days from last to definitive surgery (median (IQR))	376 (277-514)	299 (247-406)	337 (252-292)	0.313§
Mortality	1	1	2	1.000¥

† Student's t test, ‡ Chi Square, § Mann-Whitney U test,¥ Fisher's Exact Test

IQR interquartile range, sd standard deviation

Table 6.5 Patient characteristics grouped by percentage weight loss

	Percentage weight loss in previous 6 months		**Total**	**p value**
	≤ 10%	**>10 %**		
Number	17	26	43	
Age (years) (mean (sd))-	55 (15)	54 (20)	54 (18)	0.773†
Elective surgery (%)	5 (29)	9 (35)	14 (33)	0.772‡
Length of stay (days) (median (IQR))	99 (59-155)	71 (50-115)	90 (56-123)	0.293§
ITU stay (days) (median (IQR))	1 (0-19)	0 (0-3)	0 (0-7)	0.050§
Number of laparotomies (median (IQR))	3 (1-4)	3 (2-4)	3 (2-4)	0.909§
Laparostomy (%)	5 (29)	10 (39)	15 (35)	0.543‡
Days from last to definitive surgery (median (IQR))	358 (207-764)	322 (256-396)	337 (252-292)	0.616§
Mortality	0	2	2	0.502¥

† Student's t test, ‡ Chi Square, § Mann-Whitney U test, ¥ Fisher's Exact Test

IQR interquartile range, sd standard deviation

There are very few differences in the clinical characteristics between patients who were less malnourished compared to those who had more significant indices of malnutrition. There was no association between patients with a BMI ≤20 kg/m^2 and the number undergoing elective surgery, length of stay, number of laparotomies and time from last to definitive surgery (p= 0.888, p=0.599, p=0.644 and p=0.313) respectively. Similarly there were no associations between percentage weight loss and these outcomes. However, there was a trend for a lower degree of weight loss and an association with a BMI of >20 kg/m^2 relating to longer stays on ITU (p=0.050 and p=0.028 respectively).

It is perhaps surprising that objective markers of malnutrition, weight loss and low BMI, were not associated with worse clinical outcomes. It is likely that this is attributable to the fact that in type 2 IF both sepsis and the complexity of internal anatomy have a greater magnitude of effect on outcome than nutritional status. In this study the average patient age is relatively young, suggesting fewer long-term comorbidities and therefore potential for metabolic flexibility and tolerance of weight loss. However, the total number of patients was small and it would seem logical that in a larger cohort nutritional status would have an influence on outcome measures.

6.2.2.3 Nutritional management

At the point of referral 38 patients were receiving parenteral nutrition, after management by the intestinal failure team 17 patients (45%) were subsequently weaned on to oral nutrition with oral nutritional supplements and/or hypertonic saline drinks. At some stage during the index admission all patients received a period of PN. The indications for TPN in the index admission were short bowel 19 (43%), enteric contents fistulating into abscess cavity 14 (32%), obstruction 8 (18%), malabsorption 2 (5%) and anastomotic leak 1 patient (2%). During the course of the index admission 17 patients received enteral tube feeding and 2 patients underwent fistuloclysis.

In this cohort of patients there were seven episodes of CRS as in-patients in the 30 months of this study. 9 patients (19%) had one or more catheter related venous thrombosis, all of which occurred in hospital. Invariably patients had abnormal liver function tests at one point during their treatment. In 20 patients (45%) this persisted to the extent it required changes to the PN formulation beyond cyclical feeding and lipid free days.

In the patients discharged home prior to definitive surgery 22 of the 26 patients required HPN to enable discharge, The remainder were managed with a combination of oral nutrition with nutritional supplements including electrolyte mix solution, one patient also required additional overnight enteral tube feeding.

6.2.2.4 Anatomy

The presence of enterocutaneous fistulae was identified in 26 patients, with a further 2 patients having enterovesicular fistulation and 1 patient with enteroenteric fistulation and interloop abscess. In 17 patients the fistulae originated from the small bowel, 4 patients had both small bowel and colonic fistulae, 3 patients had small bowel fistulae involving the pancreas and 2 patients had colocutaneous fistulae. The fistulae output was initially high volume (>500 mls/24 hours) in 21 (81%) patients and 5 had a low volume output. 17 (65%) of patients with an enterocutanous fistulae had a laparostomy, which equates to a laparostomy being present in 35% of all patients. The presence of a laparostomy was not associated with increased length of stay

(p=0.280), ITU length of stay (p=0.423), duration of time from last laparotomy to definitive surgery (p=0.460) or nutritional status (%weight loss p=0.117 or BMI p=0.645).

There were no differences between patients with ischaemia and malrotation and all other patients with respect to age, length of stay, days on ITU, number of laparotomies, time from last to definitive laparotomy (table 6.6). There were statistically significant differences with regard to the fact that patients with ischaemia were all emergency admissions (p=0.033) and none had a laparostomy (p=0.014).

Table 6.6 Patient characteristics grouped by ischaemic aetiology

	Ischaemia	**Other causes of type 2 IF**	**Total**	**p value**
Number (%)	9	39	48 (100)	
Age (years) (mean (sd))	62 (19)	53 (19)	54 (19)	0.579†
Elective surgery (%)*	0	14	14 (33)	0.033‡
Length of stay (days) (median (IQR))*	97 (23-144)	76 (56-119)	90 (56-123)	0.938§
ITU stay (days) (median (IQR))*	7 (0-17)	0 (0-3)	0 (0-7)	0.068§
Number of laparotomies (median (IQR))	2 (1-4)	2 (2-3)	3 (2-4)	0.342§
Laparostomy (%)	0	17	17 (35)	0.014‡
Days from last to definitive surgery (median (IQR))	338 (255-489)	337 (252-492)	337 (253-492)	0.938§
Mortality	0	2	2	0.341¥

*only analysed for 44 patients with an index admission

During the course of the index admission 7 patients underwent non-reconstructive surgery under the care of the IF team, to manage complications. This non-definitive surgery consisted of 5

laparotomies for uncontrolled abdominal sepsis (as described above), one laparotomy to repair abdominal wall dehiscence and one refashioning of a prolapsing stoma.

Analysis was undertaken to assess potential differences between patients referred from within this hospital and those from other hospitals. There were no significant difference in proportion of patients developing type 2 IF following elective surgery in each group (p=0.858). The median length of stay in this hospital for patients who were regional referral was shorter 76 (56-107) versus 96 (46-153), although this not reach significance (p=0.536). There were no significant differences in any of the variables assessed, suggesting the two populations were the same (table 6.7). It should be noted that 4 of the 'local' cases although residing in the immediate catchment area, were receiving other tertiary treatment at this hospital prior to the diagnosis of IF.

Table 6.7 Patient characteristics grouped by regional versus local differences

	Local	**Regional**	**Total**	**p value**
Number (%)	19 (40)	29 (60)	48 (100)	
Age (years) (mean (sd))	53 (18)	52 (19)	54 (19)	0.755†
Elective surgery (%)	6 (32)	8 (28)	14 (33)	0.858‡
Length of stay (days) (median (IQR))	96 (46-153)	76 (56-107)	90 (56-123)	0.536§
ITU stay (days) (median (IQR))	0 (0-9)	0 (0-2)	0 (0-7)	0.577§
Number of laparotomies (median (IQR))	2 (1-3)	3 (2-4)	3 (2-4)	0.303§
Laparostomy (%)	7 (37)	10 (35)	17 (35)	0.867‡
Days from last to definitive surgery (median (IQR))	307 (244-517)	340 (253-448)	337 (253-492)	0.732§
Mortality	0	2	2	0.502¥

† Student's t test, ‡ Chi Square, § Mann-Whitney U test, ¥ Fisher's Exact Test

6.2.2.5 Mortality during index admission

There were two deaths (4.2%) that occurred during the index admission; one in a patient with intestinal ischaemia transferred from a local hospital after a 98 admission, whom on admission was identified as having multi-organ failure and died within 8 days of transfer despite intensive care input. The other was a lady with advanced neuroendocrine tumour and liver metastasis who had undergone a sub-total enterectomy and subsequently developed an enterocutaneous fistulae. She had recurrent intra-abdominal sepsis and despite multiple radiological drains and antimicrobial therapy died of overwhelming sepsis, she was too frail for surgical intervention.

6.2.3 Clinical outcomes

At the end of the study period 37 (77%) of the 48 patients had undergone reconstructive surgery. 5 (10%) patients were in the community recovering from their acute presentation in whom surgery is considered very likely and 3 (6%) patients who were considered too high risk or unlikely to gain significant benefit from further definitive surgery and were managed with low volume fistulae. 1 (2%) patient required radiological intervention as definitive treatment without recourse to surgery and there were 2 (4%) deaths.

6.2.3.1 Reconstructive surgery

At the end of the study 37 patients had undergone reconstructive surgery, this included 12 (32%) who underwent surgery during the index admission. The median time from last laparotomy to reconstructive surgery was 337 days (interquartile range 252-492), with a minimum duration of 126 days. The median time from first assessment to definitive surgery was 216 days (interquartile range 67-322). The median length of stay in those admitted electively for definitive surgery was 22 days (interquartile range 12-45).

36 patients had only one laparotomy (97%), one patient had a repeat laparotomy 9 days following definitive surgery due to a possible focus of sepsis on CT imaging, which was not confirmed at subsequent surgery. The median ASA score was 2, with a median operating time was 330 minutes (interquartile range 210-445). There were no unplanned admissions to critical care, no deaths and no readmissions within 30 days of discharge.

The median duration of follow-up from definitive surgery was 320 days (interquartile range 163-566). After hospital discharge there was 1 (5%) enterocutaneous fistulae recurrence within 2 months of surgery which healed spontaneously following intravenous antibiotics, without further recurrence at the end of the study.

6.2.3.2 Nutritional outcomes

At the end of the study after reconstructive surgery only 2 out of 37 (5.4%) patients required artificial nutrition. 18 (82%) out of 22 patients receiving HPN during a planned recovery period underwent reconstructive surgery, following which 17 (94.4%) were independent of parenteral support. One patient receiving daily HPN preoperatively had reduced parenteral requirements to alternate day intravenous fluids with hopes of cessation of artificial support with further bowel adaptation. No other patients required long-term parenteral support following reconstructive surgery. 1 (3%) patient of the 37 was dependent on long term home enteral tube feeding due to a persistent oesophageal stricture with insufficient bowel length for a colonic interposition procedure. All patients had close follow-up initially with a specialist IF dietitian.

6.3 Discussion

This is the first study that I am aware of that reports outcomes for all patients referred to an IF centre, using predetermined categories to classify patients. These data describe the heterogeneous nature of the patients referred to regional units and the need for prolonged treatment yet low levels or mortality and good outcomes for those undergoing reconstructive surgery.

Despite a national increased awareness of IF, it remains unlikely that the number of patients referred is representative of the prevalence of type 2IF in the region served by this hospital during the 30 month study period. Instead it is likely that this cohort represents one end of the spectrum of patients with acute IF, with other cases being managed in local hospitals. The study does not, therefore, enable any conclusions to be drawn regarding the incidence of type 2IF or indeed how these patients would have been managed if this service were not available in this region.

In this study 60% of cases occurred as a result of surgical complications, with a wide spectrum of indications for the original operation. However, the number of patients in each IF surgery category were too small to allow any comparison between the groups (table 6.2). It could be argued that classifying patients into categories that have not been validated adds little to the discussion regarding management of these patients. It does however provide a framework for potentially assessing clinical outcomes for patients with different phenotypes and likely different clinical courses as the literature base expands in the future. It would also provide a useful method for assessing clinical outcomes between different IF centres and allow adjustments for case mix.

If the IF surgery categories were adopted in national reporting systems with much larger patient numbers, it may be possible to identify particular groups who require a higher level of resource and factor this into referral pathways and funding mechanisms for type 2 IF. Therefore developing a system to categorise patients could provide useful additional information leading to further improvements in patient management.

In those patients transferred from other hospitals 81% had evidence of on-going sepsis based on admission imaging and CRP. The majority of this was intra-abdominal and much of it was controlled at an early stage by radiological drainage. Sepsis was the direct cause of death in one patient and significantly contributed to the death of a second patient. The presence of sepsis was not assessed in local patients due to the potential confounding effect of early expert review. However, these data support the work of other authors in highlighting the prompt and effective management of sepsis as the cornerstone of IF practice.

During the index admission the objective clinical outcome measures were largely not affected by nutritional status with the exception of length of ITU stay. Patients with a higher BMI had a significantly longer ITU stay. This is perhaps counter intuitive although there are several factors which make this results difficult to interpret. A number of the patients in this study were obese and it is possible that the longer ITU stay was a reflection of co-morbidities, reduced physical reserves or technical difficulties in ventilating and operating on obese patients. Additionally the number of patients in both groups was small and may not be representative of type 2 IF patients as a whole.

The absence of a relationship between outcome and nutritional status is perhaps initially surprising and contrary to data in other healthcare settings. However, the median overall total percentage weight loss was only 11% with a median BMI of 22, which although clinically significant is not particularly dramatic. However this cohort only represents those patients with type 2 IF referred to a specialist centre and there are no data regarding those who did not receive specialist input. Therefore if this study were undertaken with a big enough sample, it is possible nutritional status would become a predictor of outcome.

There are many other factors that undoubtedly influence the modest weight loss identified in this study. It was difficult to ascertain changes in body composition from premorbid baseline, of which weight and weight loss are surrogate markers. The majority of these patients had undergone major abdominal surgery and as a consequence of intravenous fluid replacement in the context of sepsis will have retained a significant amount of fluid. It is difficult to then accurately assess ‘weight loss’ as many patients will have retained 5-10kg of fluid, particularly when critically unwell. Weight measurements change daily and are also influenced by recent

intravenous fluid administration and fluid shifts. Therefore, with so many potential confounding factors influencing the assessment of weight loss at the point of referral to the IF team, it is possible to understand why this measurement may not correlate with clinical outcome. However, this is potentially true for all studies which use this as an objective measure of nutritional status.

This study appears to support the work of other experts, suggesting that a structured approach to the management of type 2 IF has real benefits on reducing mortality. This mortality in the series is 4 % with no operative mortality. One of the two patients who died was transferred from the referring hospital after a protracted admission with multiple organ failure and only survived 8 days and therefore although included was not representative of the cohort and serves to illustrate the need for early access to specialist centres. The mortality data compares favourably with that reported from other regional and national units 7.3-10.8% with operative mortality of 2.9-8%, albeit these are series exclusively reporting patients with enterocutaneous fistulae (34, 35, 55, 168).

The surgical outcomes from this study are very favourable compared to other studies with respect to recurrence rates, nutritional autonomy and mortality. In the sub-group of patients with enterocutaneous fistulae undergoing definitive surgery only one of the patients (5%) had a recurrence, this compares to 13-34.9% reported from other centres, despite the high proportion of patients in this study with a laparostomy (34, 35, 55, 168).

The timing of reconstructive surgery appears to play a key role in determining patient outcomes and these data support the conclusions of others that definitive surgery is best undertaken many months after the last laparotomy. The median time in this study was 11 months (55). However, this is in contrast to Brenner et al who identified higher rates of fistulae recurrence in patients with delayed surgery, although the causes of this were unclear(168).

The rationale behind delayed surgery is that once sepsis has been treated it allows resolution of abdominal adhesions and 'neoperitonealisation', combined with recovery of nutritional and physical reserves. The IF team believe that where possible this should be done in the community to aid psychological recovery. In order to achieve this it is important to have an extended multidisciplinary team, with close collaboration between physicians and surgeons. These data demonstrate that at the point of referral most patients have had several attempts at surgical repair and insufficient time has elapsed to allow a further attempt at definitive surgery without increasing the risk of further iatrogenic damage.

In this study 22 (79%) patients who were discharged home prior to definitive surgery required HPN as a bridging measure, which included 5 patients with short bowel as a result of ischaemia.

This may seem excessive but the patients initial clinical state with regard to likelihood of successful earlier reconstructive surgery and the good overall end results need to be taken into consideration.

There are undoubted clinical and financial benefits in discharging patients from hospital and allowing recovery to occur at home where possible. It also frees up bed space for other patients in need of treatment in specialist centres. Whilst this is an expensive treatment option it should be considered in the context of the overall results, in that only one of the 37 patients in this series required long-term parenteral support (intravenous fluids) at the end of the study. These data are in keeping with the outcomes reported by Datta et al, where following definitive surgery no patients were dependent on PN (34). Therefore the longer term cost savings for the wider economy will be greater if the operative success rates are higher. These data would support delaying reconstructive surgery until physical recovery was well and truly established.

In this study the number of subjects was small and there was significant diversity in the patient cohort with regard to underlying diagnosis, comorbidities, IF surgery classification and acuity at time of referral. These limitations highlight the difficulties in reporting real world data and differentiating the benefits of treatment in an specialist IF centre compared to a general hospital. This is compounded by the lack of published data at a national level which if available would allow comparisons of populations and outcome measures.

These data following reconstructive surgery and or completion of treatment suggest that low levels of complications can be achieved. The outcomes measures suggested by ASGBI highlighted in the literature review; unplanned re-operation, recurrence of fistulation, nutritional independence, mortality and unplanned readmission to ITU and hospital, seem to be very appropriate quality indicators. As more outcome data are published it would be possible to identify specific standards for these measures and refine the criteria in the future to ensure universally high standards and improve IF care.

Chapter 7: Treatment costs in type 2 intestinal failure

Most type 2 IF occurs following severe complications from abdominal surgery or an abdominal catastrophe. Patients are usually very unwell and metabolically unstable and often have complex issues relating to intra-abdominal infection, nutrition and vascular access complications. Most therefore require hospital treatment for many weeks or months and to do this safely needs an extended multidisciplinary team with true medical and surgical IF expertise.

Despite it being clear that IF patients have prolonged admissions with complex care needs, very little is known about the real financial and resource implications of managing patients with type 2 IF in UK hospital settings. As described in the literature review, the existing NHS PbR funding structure does not specifically capture cases of IF and there is no specific funding within this mechanism. Therefore it is likely that a significant funding gap exists between costs incurred by individual hospitals treating these patients and the income received. It is currently proposed that a limited number of national IF centres are identified for England working within an IF network to enable patients access to specialist expertise but this will entail selected hospitals to increase the volume of work undertaken. With the existing tariff structure, this will result in an income shortfall for those IF centres and therefore a sustainable funding mechanism needs to be in place to support this activity.

This retrospective study was designed to assess the resources and treatment costs of providing IF services in patients who had received treatment in a single regional centre. These costs were compared to the income received by the hospital for each admission to evaluate any potential shortfall. In addition the study aimed to consider the types of admission with regard an admission for assessment and stabilisation compared to an admission for complications or a planned admission for reconstructive surgery and whether the costs varied between these categories.

7.1 Methodology

7.1.1 Patient selection

Twenty five patients with type 2 IF receiving treatment at a single institution from 1st January 2010 to 31st December 2011 were selected at random from the intestinal failure database using a 'manual lottery' method. Patients were managed by the multidisciplinary intestinal failure team consisting of physicians, surgeons, specialist nurses, senior pharmacists and dietitians. Each

admission analysed was complete but some patients who were included in the study were subsequently due planned elective reconstructive surgery at a later time point. Although these patients were yet to complete all their treatment, they were included due to the protracted time course of type 2 IF management, variable timings in reconstructive surgery and the focus of the study being cost rather than clinical outcome.

7.1.2 Admission category

Patients were broadly classified to reflect the type of admission based on whether this was an index admission (IA), the patients first admission for assessment and stabilisation, an unplanned readmission (RA) for complications or a surgical admission (SA), a planned admission for reconstructive surgery. These categories were identified based on the experience of the IF team, rather than any published guidelines. Patients were also categorised according to the IF surgery criteria that they had undergone or were likely to undergo to ensure the study population reflected the spectrum of patients with IF (table 2.2).

Patients were also categorised to reflect differences in activity between patients who were local (to this institution) and developed complications during their admission, resulting in a diagnosis of type 2 IF and those who were regional IF referrals.

7.1.3 Data collection

Clinical information was retrospectively collected from electronic and paper records with regard to age, gender, diagnosis and clinical outcomes.

Using internal institutional IT systems a structured comprehensive search was undertaken for each hospital admission to record all clinical activity that was captured electronically in various hospital databases which included costs for; bed days, critical care, radiology, operations, pathology costs and high cost drug items.

- Costs for critical care, high cost drugs and devices (individually priced procedures, drugs and devices- IPPDD) are determined by central NHS funding bodies and are charged separately to other aspects of care. Therefore hospitals are potentially able to recoup all of these costs separately compared to other variable costs which rely on HRG codes. These types of costs were identified for each admission from data recorded on the hospital electronic system. Data are presented with and without critical care and IPPDD costs. No other drug costs were included as these are not electronically recorded.

- Bed day costs were calculated by using the length of stay in days (minus the number of critical care bed days) and multiplying by local figures for bed day costs.
- Costs for surgery were calculated using duration of operation time in minutes multiplied a locally adjusted cost per minute of £15.00. This is a nationally recognised model for assessing surgical costs. No adjustments were made for dual consultant operating.
- Radiology costs were based on nationally set tariffs per procedure. Importantly no costs for interventional radiology were included as these were not recorded electronically.
- The income received by the institution was identified from electronic billing records.

7.1.4 Specialist staffing costs

It is considered that one of the biggest resources in IF service provision relates to the use of specialist staffing costs, in particular the demand on the intestinal failure team (3, 25). It was not possible to capture this electronically but as it is recognised as such a critical component of the care provided on a daily basis we chose to model this based on activity of the core team members.

Each member of the IF team was asked to estimate how much time they would spend per patient per week undertaking the various components of a typical admission (table 7.1). The total time taken each week for each core member of the IF team was then multiplied by mid-point salary scales to estimate a cost per patient per week. This was then applied to each individual admission based on length of stay.

This modelling was not extended for other specialists which are often heavily involved in some patients but whose input varies considerably between patients e.g. tissue viability nurse, stoma nurses, psychologists, microbiologists, pain services and interventional radiologists.

Table 7.1 Clinical activities of the core members of the IF team

Transfer liaison	Catheter care management
Assessment	Patient training
Discharge planning	Liaison with home care companies
Daily/ (weekly) review	Pharmacy liaison
Co-ordination of ward care	

7.1.5 Statistical analysis

Results are presented as mean and standard deviation for normally distributed data, and median and range for non-normally distributed data. Comparisons between groups were made using students t-test, the distribution regarding length of stay and total costs between the categories were compared using Kruskal Wallis analysis and p-values less than 0.05 were considered to be statistically significant. Statistical analysis was carried out in SPSS version 18.

7.1.6 Ethical approval

We did not feel that ethical approval was required for this cost study.

7.2 Results

7.2.1 Demographics and aetiology

25 patients (12 female) were included in the analysis, complete data were available for all. The median age on the first admission was 58 years. 17 patients were regional referrals, 15 (88.2%) of which required an acute transfer. The underlying aetiology was a result of surgical complications in 15 (60%), Crohn's disease 5 (20%) and mesenteric ischaemia 5 (20%). In patients who had type 2 IF following surgical complications the diversity of this cohort is demonstrated by the procedures undertaken in their original surgery (table 7.2)

Table 7.2 Indications for original surgery

Procedure (elective)	**Procedure (emergency)**
Reversal of ileostomy (diverticular disease) – 2 patients	Laparotomy for acute small bowel obstruction – 4 patients
Reversal of Hartmann's (diverticular disease)	Acute appendicitis
Pancreatic resection (Berger's procedure)	Small bowel volvulus
Repair of enterocutaneous fistulae	Diverticular perforation (sigmoid colectomy)
Anterior resection colorectal cancer	Pancreatic necrosectomy (acute pancreatitis)
Laparotomy for chronic abdominal pain	

7.2.1.1 Type of specialist intestinal failure surgical procedure

All patients were also classified by IF surgery criteria undertaken or anticipated to be undertaken in the future, in those yet to complete treatment (table 7.3).

Table 7.3 Patient classification by IF surgery criteria

Intestinal failure surgical procedure	**Definitive surgery**	**Awaiting surgery and non-surgical intervention**
2a) Enteric fistulation associated with laparostomy (open abdomen)	4	4
2b) Enteric fistulation associated with other organs	2	1
2c) Enteric fistulation associated with abdominal sepsis requiring radiological or surgical drainage	2	2
2e) Enteric fistulation associated with recurrent fistulation following previous surgical attempts at repair	1	0
3b) Hostile abdomen associated with re-operation for adhesions	1	0
3c) Hostile abdomen associated with abdominal sepsis requiring surgical drainage	1	1
4) Abdominal surgery where planned operative intervention would deliberately result in a period of IF	0	1
5) Abdominal surgery where the primary aim of surgery is to restore intestinal continuity	4	1

7.2.2 Nutritional management

The requirement for PN is included in the results as an indication of the resources these patients need and hence the financial cost due to the material and human resource cost of providing this service. At the time of acute transfer to this unit 13 out of 15 (87%) patients were receiving PN at the referring hospital. At some point during the IA all patients required a period of PN. Following the IA 14 (61%) patients were discharged with home artificial nutrition support (13 HPN and 1 enteral tube feed) to enable discharge.

7.2.3 Clinical outcomes

Of the 25 patients assessed, at the end of the study 16 were nutritionally independent, 1 patient had successfully reduced his requirements from daily HPN to alternate day intravenous fluid with the expectation of completely withdrawing parenteral support, 6 patients were awaiting IF surgery and 1 patient was managed conservatively with the intention of spontaneous fistulae closure. There was only one death, a patient transferred from a local hospital after a 98 day admission, who had multi-organ failure on admission and died within 8 days of transfer. There were no operative deaths.

7.2.3.1 Definitive surgery

At the end of the study 15 patients had undergone definitive surgery, 11 of these undertaken as planned admissions from home (SA). In addition, 4 patients underwent definitive operations undertaken during the IA, although all were performed at least 6 months after the last surgery occurred. The median operating time for all cases was 300 minutes (range 90-690), of which 5 cases (33%) involved dual consultant operating (figure 7.1). Those patients who underwent reconstructive surgery during the IA appeared to have significantly longer procedures, although there were only 4 patients in this group.

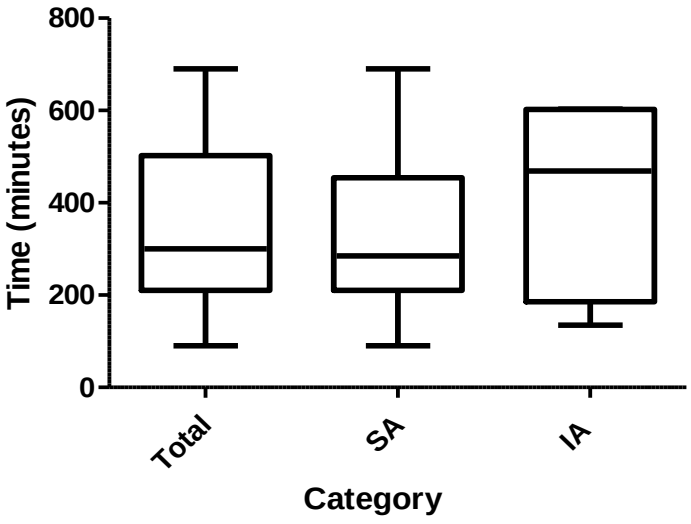


Figure 7.1 Duration of operation for definitive surgery classified by type of admission

7.2.3.2 Non reconstructive surgery

During the course of the IA, 5 patients underwent unplanned non-definitive surgery under the care of the IF team, to manage complications. This non-definitive surgery consisted of 3 laparotomies for uncontrolled abdominal sepsis, one laparotomy for abdominal wall dehiscence and one refashioning of a prolapsing stoma.

7.2.4 Admissions

The treatment of these 25 patients resulted in 65 admissions, of which 4 were excluded from more extensive cost analysis, as these were either related to day case procedures or ward reviews (table 7.4).

Table 7.4 Number of patient admissions recorded by admission type and geography

Type of admission	**Type of patient**		**Total**
	Local, n (%)	**Regional, n (%)**	
Index	8 (13)	15 (25)	23 (38)
Readmission	7 (11)	20 (33)	27 (44)
Reconstructive surgery	5 (8)	6 (10)	11 (18)
Total	20 (33)	41 (67)	61 (100)

7.2.5 Length of stay

The management of these 25 patients and ensuing complications resulted in a total of 3139 bed days at this institution, equivalent to 8.6 beds per annum at 100% occupancy. The median length of stay was 51.5 days (range 1-297), with considerable variation in length of stay between each category (table 7.5). There was a significant difference in the distribution of length of stay between the IA, RA and SA groups, $p<0.001$ (figure 7.2).

Table 7.5 Length of stay categorised by type of admission

Type of admission	**n**	**Length of total stay (days)**	**Median length of stay (days)**	**Range**
Index	23	2249	94	8-297
Readmission	27	423	7	1-75
Reconstructive surgery	11	467	28	7-137
Total	61	3139	51.5	1-297

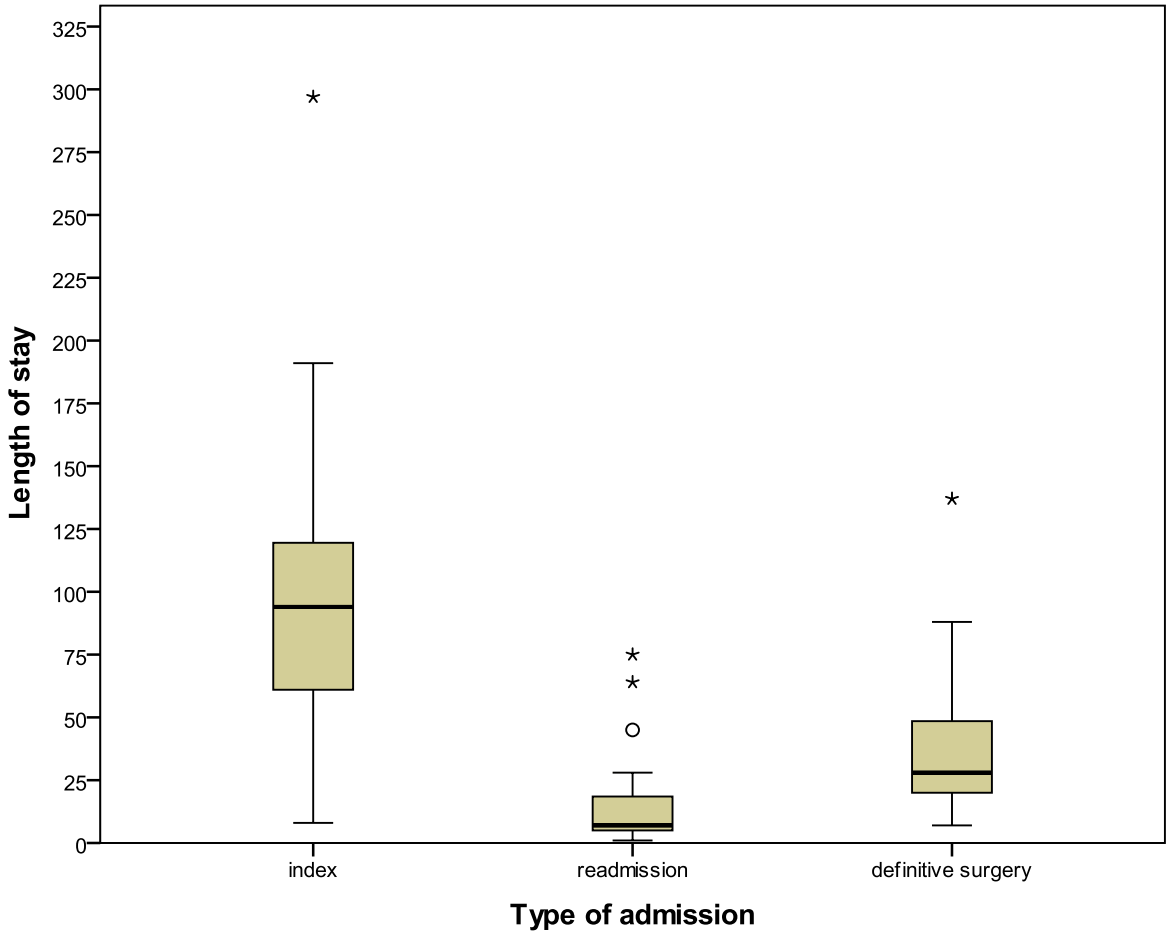


Figure 7.2 Length of stay categorised by type of admission

There were differences in median length of stay at this institution on IA between local and regional referrals, 119.5 versus 73 days respectively, although this did not reach statistical significance (p=0.061). The 15 regional patients transferred acutely had a median length of stay of 75 days (range 20-366) at the referring hospital prior to transfer. The median total length of stay for regional referrals (the duration at both referring and this hospital) was 136 days (range 57-439). There was no statistical difference between the total length of stay of local versus regional patients 119.5 v 136 days (p=0.232) in the IA. Four regional patients underwent definitive surgery during their IA. The total length of stay of these patients at this centre was 440 days (median 88 days).

The IA also resulted in the longest stay in critical care, median 6.5 days (range 0-37). None of the patients readmitted required a critical care stay, whereas all patients undergoing SA were managed electively in critical care beds post-operatively due to the nature of the surgery, although the time period was relatively short, median 3.5 days (range 0-7).

7.2.6 Readmissions

There were 11 patients who were readmitted a total of 27 times (see table 7.6). Only 3 readmissions were within 30 days of discharge and none followed reconstructive surgery; one as a result of an intravenous catheter related complication, one as a result of low grade intra-abdominal sepsis and one as a result of abdominal wall infection.

Table 7.6 Indications for patient readmission

Indication for readmission	**Frequency**
Catheter related complications	8
Abdominal wall/wound infections	6
Recurrent low grade intraabdominal sepsis	3 (one patient)
Obstruction (conservative management)	3
Short bowel syndrome	3
Recurrence of spontaneous Crohn's enterocutaneous fistulae with no previous operative intervention	2 (one patient managed conservatively)
Elective cholangiogram and stent change	2

7.2.7 Costs

The total cost of the IA was the greatest, with the cost of the RA and SA being considerably less (table 7.7). There was a statistical difference between the distribution of total costs between the three categories ($p<0.001$), this was the case if critical care and IPPDD costs were included or excluded. The total amount received by the Hospital in terms of income was 44.7% of the predicted costs, after critical care and IPPDD costs were excluded. Therefore there was a significant difference in the actual costs compared to those predicted in this study. There is considerable variation in the ability to recover costs between the three different types of admission; IA 41.4%, RA 75.6% and SA 34.0%. There were no differences with regard to the proportion of income received compared to predicted costs for local patients (53.7%) and regional referrals (50.1%).

Table 7.7 Total costs of treatment categorised by type of admission

Type of admission	Total income	Total income excluding critical care and IPPDD	Total predicted costs (containing figures for ITU/HTU stays and IPPDD)	Median predicted cost (containing figures for ITU/HTU stays and IPPDD). (range)	Total predicted costs (minus ITU/HTU and IPPDD)	Percentage of total expenditure recovered (excluding critical care and IPPDD)
IA	£ 656,678	£ 381,693	£ 1,270,144	£55,223 (6,249-138,703)	£ 920,928	41.4%
RA	£ 122,713	£ 139,091	£ 218,048	£8,075 (824-37,273)	£ 183,873	75.6%
SA	£ 160,955	£ 84,771	£ 333,021	£30,274 (7,512-69,846)	£ 249,227	34.0%
Total	£ 940,346	£ 605,556	£ 1,821,213	£17,208 (824-138,703)	£ 1,354,027	44.7%

7.2.7.1 Cost per day

To standardise the cost of an admission, recognising the heterogeneity in the patient cohort and variable length of stay, we have estimated a cost per day and compared this to current income received (table 7.8). When expressed as a cost per day, these data highlight considerable variations in the income received by the hospital across all three admission categories range £146-£6788. These costs are the figures based on the NHS HRG codes by which the hospital is paid and independent of this cost study.

Whilst all SA admissions accounted for only 18.3% of the total estimated expenditure, it is clear that the cost per day is actually very high and it is the admission type with the largest difference between income and predicted costs. In this study only 11 patients had a planned admission for reconstructive surgery compared to 23 index admissions. If more surgical admissions had been included in the analysis then the funding gap may be larger.

Table 7.8 Cost of treatment per day categorised by type of admission

Type of admission	Median income cost per day including critical care and IPPDD (min – max)	Median predicted cost per day, including critical care and IPPDD (min-max)	Median predicted cost per day excluding critical care and IPPDD
IA	£305 (£150 - £737)	£470 (£431 - £1012)	£442 (£354– £833)
RA	£760 (£146 - £6788)	£619 (£414 - £1227)	£468 (£360 - £1067.27)
SA	£493 (£237 - £1015)	£843 (£498 - £1073)	£726 (£418 - £933)

The IA utilised the largest number of radiological procedures compared to other admission categories. In an IA the mean number of CT scans was 2.9 (standard deviation 2.6) and it also resulted in the heaviest use of fluoroscopic interventions, ultrasounds, magnetic resonance imaging and blood transfusions (table 7.9).

Table 7.9 Utilisation of resources categorised by type of admission

Type of admission	N	Number of CT scans and interventions Mean (sd)	Number of fluoroscopic investigations and Interventions Mean (sd)	Ultrasound scans/ interventions Mean (sd)	MRI Mean (sd)	Blood transfusion Mean (sd)
IA	23	2.9 (2.6)	2.1 (1.9)	1.0 (1.1)	0.3 (0.8)	3.7 (3.8)
RA	27	0.7 (1.2)	0.8 (0.8)	1.1 (0.5)	0.0 (0.3)	0.9 (1.1)
SA	11	0.6 (0.9)	0.8 (1.1)	1.1 (1.6)	0.0 (0)	2.6 (2.1)
Total	61	1.5 (2.1)	1.2 (1.5)	0.6 (1.1)	0.1 (0.5)	2.3 (2.9)

sd standard deviation

RA proportionally placed the greatest demands on the time of the intestinal failure team, which accounted for an average of 24% of the admission costs. Although the median length of stay of a readmission was short, it required considerable logistics to coordinate but relatively small use of high cost drugs and no critical care use. Patients undergoing SA proportionally required the least input from the intestinal failure team time, other than the surgical aspect. The proportion of the total cost accounted for by actual operative cost in the SA is estimated to be 31.1%, compared to 4.1% in the IA and 0% in the RA groups.

7.3 Discussion

This is the first study I am aware of which has set out to assess the resources used in patients with type 2 IF and estimate the cost of managing these complex patients. This study demonstrated that the inpatient care required by patients with type 2 IF varies considerably from patient to patient, as indicated by the variation in length of stay (8-297 days) and cost per day (£414 - £1227). These data have demonstrated that there are statistically significant differences in the distribution of length of stay and cost by admission type.

In this study there was a considerable range in the costs and length of stay, indicating the heterogeneity of the patients and variable nature of the care required, suggesting that a non-specific fixed price tariff structure is unlikely to reflect this activity. This is significantly different when compared to patients with other more predictable conditions and shorter length of stay. This should be considered in future tariff structures. This study also highlights significant variations in the existing NHS tariff structure when applied to type 2 IF patients, most noticeable when expressed as a daily rate, varying from £146-£6788. Therefore there are considerable inconsistencies with the current mechanisms through which IF is coded.

One of the most surprising findings was the amount of time regional patients spent in their referring hospital prior to transfer, median length of stay of 75 days (range 20-366). This is despite all referrals being admitted to this institution within 10 days of referral. There are several possible explanations for this including; clinicians only referred the more 'complex' cases, those who survived their initial insult or those whom they felt required HPN.

It is likely that the costs of treating patients in specialist IF centres is higher than in general hospitals due to the additional staffing and nature of radiological and surgical interventions. A proportion of these patients will also require a period of HPN prior to reconstructive surgery. However, it is possible that the overall costs to the health economy are offset or in indeed may be reduced by early referral to an IF centre given the likely significant costs incurred by general hospitals as suggested by the protracted time prior to referral.

This study has demonstrated that the existing tariff structure in the UK results in significant funding gaps, with hospitals at best only recovering 44.7% of their costs. This is based on a conservative estimation of the resources required to manage these types of patients and in reality the deficit is likely to be much higher. This is despite members of the IF team working closely with members of the clinical coding (recharging team) to maximise income recovery. It is therefore unlikely that the current funding mechanisms will ever be sufficient to allow IF centres to completely recover their costs.

These funding deficits are most pronounced in definitive surgery, where only 34% of costs are recovered. One of the reasons behind this is the lack of appropriate NHS tariffs available to describe the operations that are performed. The median operative time in this cohort was just more than 5 hours. The surgery is often complex with 33% of cases requiring 2 consultants of differing specialities working together. However, often the only tariff available to describe this type of operation is a small bowel resection, clearly an inadequate description of the complex surgery and post-operative care that occurred and therefore this is not appropriately costed.

An alternative funding mechanism would be to introduce a tariff based on a daily rate. This would take into account the variability in patient cohort, some of the demand for resources and variable length of stay. A tariff based on the category of admission would also take into account the high costs of definitive reconstructive surgery admissions, although the actual operating costs are a relatively small component of the total expenditure.

A similar approach to funding was considered in the original HIFNET document in 2006(5). The figure proposed in the HIFNET document was £757 per day, however this appears to have been based on only one patient during an index type admission. Reviewing the HIFNET cost breakdown there are a number of areas which may explain some of the differences. The HIFNET costing would appear to have been undertaken by a detailed notes review and therefore more likely to capture individual patient differences such as drug costs and review by specialists other than the IF team. The HIFNET patient had 17 hours of theatre time suggesting several operations were undertaken which may have included reconstructive surgery. There was a longer duration of critical care stay 22 days compared to a median of 6.5 days in this study

The differences in methodology, patient differences and inclusion of costs not recorded in this current study likely explain the differences in cost per day from the HIFNET example. Although the overall cost per day was higher than the median in this study it was within the range identified for an index admission. The HIFNET report commented on the difficulties in identify the costs of treating type 2 IF, which in their view precluded the use of tariff based commissioning currency for IF services. Further work in assessing funding mechanisms was recommended.

Although the number of patients presented here are small, in those who have completed their treatment as a type 2 IF patient, 94% (16/17) are nutritionally independent, which prevented or stopped the need for HPN in 10 patients, all following surgery. The cost of managing patients on HPN is variable but estimated to be in the region of £50,000 to £100,000 per annum. Although the costs of managing an episode of type 2 IF, as identified in this study, are relatively high, if successfully treated the number of patients who require long term HPN are reduced, and significant long term cost savings to the wider health economy can be achieved.

Due to the many methodological limitations of this study it should not be used as a definitive costing analysis. The main limitation was that activity and therefore cost is predominantly based upon electronic data capture and therefore if clinical activity was not recorded or poorly entered on a hospital based system there was no way of identifying it or correcting it in this study. Additionally the patients were admitted over several financial years due to the protracted nature of managing type 2 IF and NHS costs change over time. Therefore, the figures presented here are

likely to represent a significant underestimate of the costs actually incurred through providing these services.

There are many components of medical care which make up a proportion of the total NHS bed day costs such as physiotherapy and occupational therapy which these patients utilise disproportionate amounts of time for. This is also the case for more specialised services such as stomatherapy, tissue viability and input from medical specialities, particularly interventional radiology. Within this model we have not been able to capture any of this activity and due to the heterogeneous nature of the patients it would require an individual case notes review costing exercise akin to the HIFNET review, across a number of regional units over an extended period of time to get more accurate data.

In conclusion, this study has demonstrated that patients with type 2 IF have prolonged hospital stays and consume considerable financial resources. Due to the type of model used, these data are likely to represent a significant underestimate of the costs actually incurred. Despite this, there was a considerable discrepancy between the predicted costs and the amount recouped through existing tariffs within the NHS. There are significant differences between the types of admission, in terms of length of stay and resulting costs. This also has implications on the percentage of expenditure that institutions are able to recoup through existing mechanisms. Therefore this study suggests future funding of type 2 IF services should be based on a cost per day model depending on the type of admission, although a more comprehensive study is needed to determine the precise value of these daily rates.

Chapter 8: Conclusions and implications for clinical practice

8.1 Challenges in intestinal failure practice

Acute IF is a common clinical problem, particularly in those patients undergoing abdominal surgery. It is best managed by a multidisciplinary team familiar with the administration of parenteral nutrition. Treatment is invasive, expensive and associated with clinical risk in the form of PN and non-PN related complications.

Much of the scientific literature regarding parenteral nutrition is difficult to interpret and apply to clinical practice. Various national and international clinical societies have developed guidelines, however there have been relatively few publications regarding quality of care and outcomes. The NCEPOD report was the first published national observational study on PN carried out in the UK and found that only 19% of adult patients received good care. They found poor standards of assessment, documentation of nutritional risk, monitoring and catheter complications.

In addition to concerns regarding the quality of clinical care there remain issues with the provision of infrastructure for intestinal failure at local and national level. Despite recommendations from various expert bodies, including NICE guidelines, that all hospitals should have a nutrition support team, the NCEPOD report highlighted that only 50% of hospitals do so. At a national level the HIFNET document in 2008 recommended the development of a structured network for providing services to patients with type2 and 3 IF in order to ensure patient access, reduce duplication of services and facilities, reduce mortality and morbidity, decrease length of length of stay and reduce the number of long term type 3 IF patients. At the time of writing this is yet to be implemented.

This thesis has described the problems relating to the published literature with regard to defining the intestinal failure and differentiating patients with type 2 IF, undoubtedly one of the factors that have resulted in a lack of reported clinical outcomes and standards of care. The ability to define type 2 IF easily in practice is important in determining how hospitals in the UK are paid for this clinical activity, which in turn is strongly linked to drives to improve quality. The results of this research are therefore relevant to current issues relating to the quality of IF care and infrastructure.

8.2 Thesis conclusions

This thesis examined these issues in acute IF by assessing the following 4 interrelated issues:

1. Specialist IF centres provide high quality of PN care and dedicated IF units improve clinical outcomes.

2. Identifying patients with type 2 IF in clinical practice through simple screening tools will potentially aid diagnosis and early specialist input. IF surgery criteria are applicable and relevant to clinical practice.

3. Assessing clinical outcomes in a cohort of patients with type 2 IF and the potential quality indicators for improving practice in the future.

4. The treatments costs of managing patients with type 2 IF have been assessed and alternative funding mechanisms have been identified.

8.2.1 Assessing quality of care in acute intestinal failure

This thesis reported data relating to the PN care in 50 patients with acute IF, examining outcomes based on those assessed by NCEPOD. The results demonstrated that in a hospital with an established infrastructure and experience in managing PN, a member of the NST was involved in 90.0% of the decisions to start PN compared to 52.7% nationally. It would seem logical to assume that this was the main reason for the reduced proportion of patients receiving inappropriate PN, 4% in this study compared to 29% nationally, reducing potential risks and costs.

Despite the high standards of assessment and decision making, this study highlighted there were still issues with regard to catheter documentation and biochemical monitoring. This encompasses some of the main challenges in acute IF, the involvement and co-ordination of numerous clinical teams and health care professionals to deliver timely and safe clinical care.

This research also reported improvements in other aspects of PN care observed on a dedicated IFU. The study demonstrated significant differences between the volumes of PN recorded compared to the amount administered with some significant errors noted, although standards on the IFU compared to other wards were better. Managing patients in a dedicated unit resulted in significant improvements in the rates of CRS, reducing the incidence from 10.01 episodes per 1000 PN days to 1.80 episodes per 1000 PN days in the space of 2 years.

This study has demonstrated that overall high standards of PN care can be achieved in acute IF although some aspects of clinical practice could have been improved upon further. Therefore it is

essential that all hospitals managing IF should periodically audit their own clinical practice in a similar fashion to NCEPOD to ensure safe and effective care is being provided. This would be labour intensive if undertaken continuously but in day to day practice CRS rates would be easier to monitor and could be used an on-going marker of PN care. It would seem appropriate for the relevant health commissioners to set standards of CRS rates which hospitals should be judged against.

8.2.2 Criteria for diagnosing type 2 intestinal failure

One of the main challenges in the development of intestinal failure practice had been establishing a consensus definition and wider recognition of the sub classification, which until recently was largely confined to specialist hospitals within the UK. Despite these recent developments, in clinical practice there are likely to be ongoing difficulties interpreting these definitions, particularly by non-specialists, and hence an inability to identify patients with more complex IF that are potentially best managed in regional units.

The results from this study have demonstrated that PN treatment for more than 28 days can be used as a screening test for identifying patients with type 2 IF with high sensitivity but lower specificity. Although there are significant methodological difficulties in this study, it does stand to reason that longer courses of PN are associated with more complex intraabdominal pathology. This study also helps to validate proposed criteria for defining type 2 IF surgery. Although neither of these two approaches are without their limitations, the use of both could help shape the development of national IF infrastructure through standardising reporting mechanisms, identifying important outcome data, the ability to benchmark clinical practice and enablement of suitable 'IF tariff' development .

8.2.3 Clinical outcomes and quality indicators in type 2 intestinal failure

There are limited published data regarding clinical outcomes in patients with type 2 IF, the available studies largely focused on patients with enterocutaneous fistulae. This study demonstrated the variety and aetiology of patients with type 2 IF referred for management to a specialist centre. Whilst the majority of patients had enterocutaneous fistulae there were a significant proportion of patients with alternative aetiologies.

This study highlights some important outcome measures which could be considered in a national reporting process. The mortality rates in this series were low, 4.2% during an acute admission. Following reconstructive surgery there were no deaths, no re-operations for disease recurrence or readmissions within 30 days and only one patient had a recurrence of fistulae. Following surgery

94% of patients were independent of artificial nutrition a useful indicator of overall management and decision making.

Defining IF surgery would allow centres undertaking these procedures to report outcome measures, which ultimately would result in improvements to patient care through refining best practice and encouraging clinical research. It is important that low rates of mortality, fistulae recurrence and high levels of nutritional independence are achieved. Monitoring of these outcomes should be an integral component in hospitals maintaining IF centre status. Improving standards not only improves patient outcomes but is also likely to result in significant cost savings, shorter length of stays and fewer patients needing long term HPN.

8.2.4 Costs of type 2 intestinal failure

Most hospitals currently manage a spectrum of patients with acute IF and it is likely that there are a few individuals with established type 2 IF treated in general hospitals. These patients require complex treatments and long periods of hospitalisation. This study has demonstrated that the costs incurred in caring for these patients vary significantly between patients and the type of admission. It has also been demonstrated that the current funding mechanisms within the NHS only allow for hospitals to recover 44.7% of the costs at best, with the real deficit likely to be significantly higher.

Due to the high treatment costs this places significant financial pressures on hospitals that provide this service at a regional level. This creates a perverse incentive to refer patients to the two nationally commissioned units, which historically at times had become overwhelmed by demand. This lead to the development of waiting lists and forcing general hospitals to manage these patients with specialist needs. Until appropriate funding and infrastructure is established for patients with type 2IF it is likely that some patients will not get the access to treatment required.

This study demonstrated that there were considerable differences in the types of admission and the costs of treatment, which may be a relevant in the way that future tariffs are determined. These data on treatment costs could be combined with the evidence in support of the criteria for IF surgery to develop an ‘IF tariff’, which could be used in designated IF centres.

8.3 Summary

In conclusion, the work presented in this thesis has demonstrated that when managed by an experienced multidisciplinary team the standards of care in acute IF can be generally high. Improvements in outcomes are potentially difficult to implement due to existing uncertainties regarding IF definitions and establishing what the quality standards are but with regular assessment of clinical practice and outcomes it is possible to identify areas for potential improvement.

This study has demonstrated that using duration of PN treatment is a potentially useful clinical tool to help screen patients who may already have or are at risk of developing type 2IF and hence enable identification of patients who would benefit from early IF specialist input. This study established that there is a significant funding gap between costs of treatment and income per patient. Until issues of definitions and funding are resolved it unlikely that regional centres will be able to continue to offer these specialist services which in this study have been shown to be both safe and effective.

Appendices

Appendix A

A.1 Quality of parenteral nutrition care case report form

Patient ID _____

Age _____ years

Gender ☐ male ☐ female

Speciality _____ Ward level ☐ Level 1 ☐ Level 2 (HDU)

Type of ward ☐ IFU ☐ other _____

Indication for PN _____

Admission type ☐ planned ☐ emergency ☐ inter-hospital transfer

Day of week PN commenced _____ ☐ planned ☐ unplanned

Person commencing PN ☐ nurse ☐ dietician ☐ pharmacist ☐ doctor

Member of nutrition team ☐ Yes ☐ No

Type of enteral feeding _____

Reason not possible to continue enteral feeding _____

Re-feeding risk criteria

Days no nutrition _____ days

BMI _____

% weight loss in past 3-6 months _____

Low levels potassium, magnesium or phosphate prior to feeding ☐ Yes ☐ No

Precautions to prevent re-feeding syndrome ☐ IV vitamins ☐ Reduced initial rate of feeding ☐ None

PN referral made date _____ time _____

PN start date _____

Appendix A

Interval between decision to start PN and commencement _____

Reason for delay _____

Days of PN _____ days

First type of PN ☐ multi-chamber ☐ multi-chamber + micronutrients

☐ multi-chamber + micronutrients + tailored additions

Completion of fluid balance charts

☐ Yes ☐ No ☐ Partially complete

Adequate biochemical and nutritional monitoring

Bloods ☐ Yes ☐ No

*adequate = baseline, daily until stable, then weekly

BMs ☐ Yes ☐ No

*adequate = baseline, 6 hourly for first 72hrs, then daily

Weight ☐ Yes ☐ No

*adequate = daily if concerns regarding fluid balance, otherwise weekly reducing to monthly

Patient Outcome

☐ Weaned onto oral/enteral feeding ☐ Home parenteral nutrition

☐ Transferred to another unit ☐ Died during hospital stay

Metabolic complications

Evidence of metabolic complications ☐ Yes ☐ No

Type of complication

- ☐ Hypophosphataemia
- ☐ Hyperphosphataemia
- ☐ Hyponatraemia
- ☐ Hypernatraemia
- ☐ Hypomagnesaemia
- ☐ Hypermagnesaemia
- ☐ Hypokalaemia
- ☐ Hyperkalaemia
- ☐ Hypoglycaemia
- ☐ Hyperglycaemia

Care of Central Venous Devices and Intravenous Feeding Catheters

How many CVCs during PN administration _____

Initial mode of PN delivery ☐ PICC ☐ Central catheter ☐ Tunnelled catheter

Catheter site documented ☐ Yes ☐ No

Reason for catheter insertion ☐ Solely for PN ☐ Venous access with 1 lumen for PN

Initial type of PN catheter ☐ multilumen ☐ single lumen ☐ cuffed ☐ uncuffed ☐ unknown

Type of catheter documented ☐ Yes ☐ No

Position of tip documented ☐ Yes ☐ No

Person responsible for inserting catheter _____

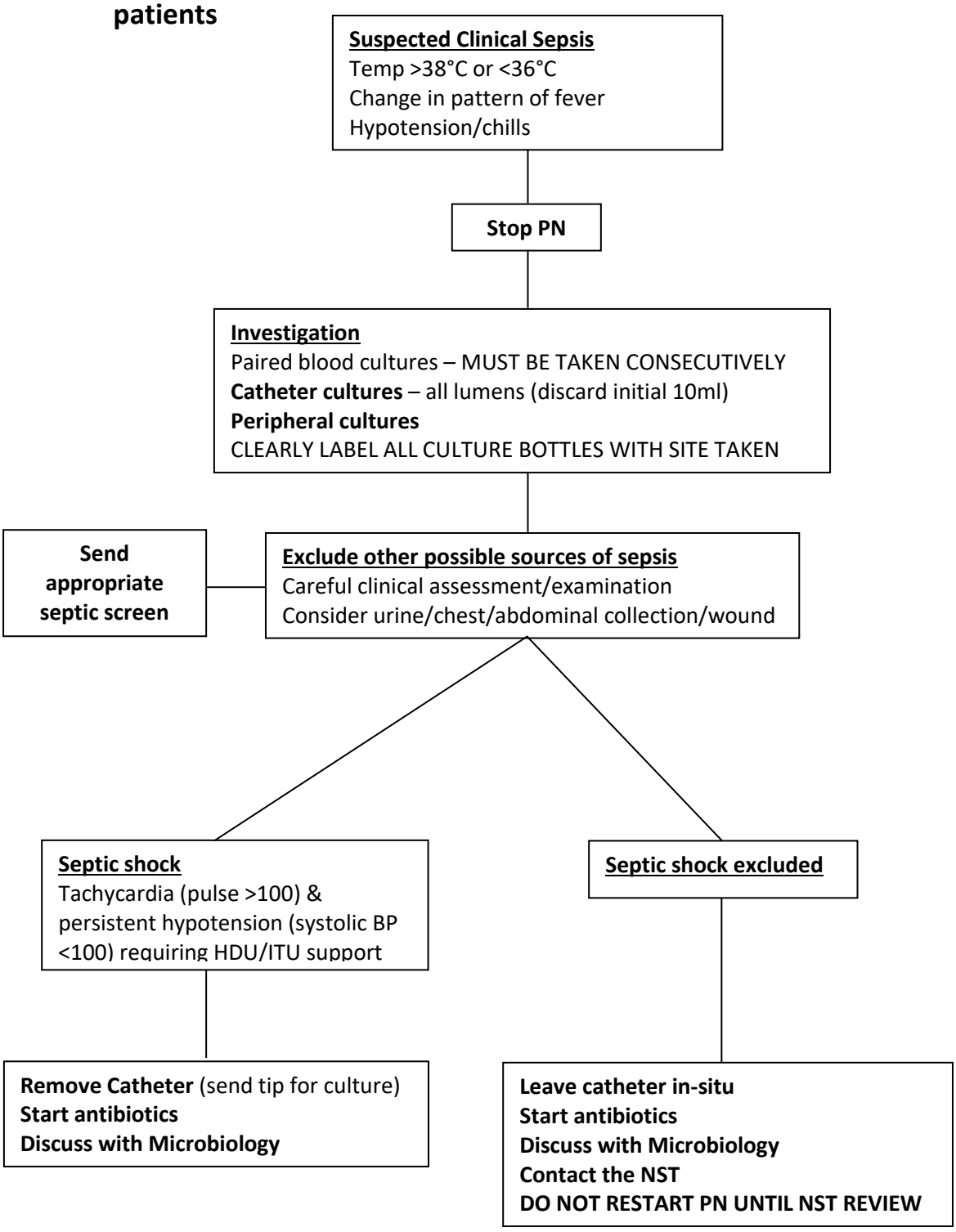
Catheter days before PN _____ days

Evidence of CVC complications ☐ Yes ☐ No

Type of complications _____

Appendix B

B.1 Protocol for managing suspected catheter-related sepsis in PN-fed patients



Appendix C

C.1 Accuracy of parenteral nutrition administration data collection sheet

			PRESCRIPTION			FBC	START	END
NUMBER	DATE	WARD	VOLUME	HOURS	ML/HR	VOLUME GIVEN	BAG WEIGHT	BAG WEIGHT

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