THE UNIVERSITY OF HULL

GUT FAILURE:
DIAGNOSIS AND MANAGEMENT

being a Thesis submitted for the Degree of Doctor of Medicine (M.D.)

in the University of Hull

by

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- The gut -

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The candidate confirms that the work submitted is his own and that appropriate credit has been given where reference has been made to the work of others

This work is dedicated to:

My wife Marika,
and
our precious daughter Klara.

For helping to kindle the flame,
and
then lovingly sustaining the blaze.

ABSTRACT

Background: Inadequate gut function (IGF) or intestinal failure (IF) is common, particularly in surgical patients and the critically ill. It is difficult to measure objectively, and as a consequence its effects on outcome are contentious and treatment options are limited. Because of the gut's numerous homeostatic functions IF may predispose to delayed sepsis and multiorgan failure (MOF), eventually resulting in death.

Aim: To review the evidence regarding the clinical importance of IF, to define this phenomenon quantitatively, determine its effects, if any, on prognosis and to develop a therapy to treat it.

Methods: A series of prospective clinical studies.

Results: The state of gut function could be defined in terms of the tolerance by the gut of ≥80% of calculated nutritional requirements for a continuous period of ≥48 hours. This was independently associated with outcome ($p<0.001$; OR 16.081; 95%CI 5.356, 48.282). The site of feeding, be this prepyloric or postpyloric, did not influence the proportion of patients that achieved tolerance (respectively 23/33 [70%] vs. 19/32 [63%]; p=0.539). Administering a cocktail of gut-specific nutrients (GSN) expedited the return of gut function when compared to controls (respectively 164 [120–225] hours *vs.* 214 [184–401]; p=0.016), attenuated the stress response (serum albumin respectively p=0.048 *vs.* p=0.054), decreased sepsis (respectively 4/25 [8%] *vs.*13/25 [52%]; p=0.015), and the absolute number of deaths (2/25 [8%] *vs.* 7/25 [28%]; p=0.138, not significant).

Conclusion: Adequacy of gut function can be defined quantitatively by enteral tolerance. Characterized in this way, IF is independently associated with prognosis, irrespective of other single organ failures and other determinants of outcome. GSN stimulate the return of gut function and this is associated with improved outcomes. Further research and the development of other gut-directed therapies are necessary.

STATEMENT OF ORIGINALITY

This thesis has been prepared by the candidate. The work comprises a review of the relevant literature, 7 original studies (3 randomized clinical trials and 4 observational studies) and one reanalysis of data from a previously published study. The investigative work described in this thesis was performed solely by the candidate, except where clearly stated. Appropriate credit has been given where reference has been made to the work of others. This thesis work has not been submitted for any other degree or professional qualification.

Publications and academic recognition as a result of work from this thesis are listed in appendices 1 and 2 respectively.

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ABBREVIATIONS

A number of abbreviations have been used throughout this thesis. These are summarised here in alphabetical order. The first time an abbreviation appears, it is preceded by the words for which it stands.

APACHE	Acute physiological and chronic health evaluation (score)
ASA	American society of anaesthesiologists (grading)
BAPEN	British association of enteral and parenteral nutrition
BMI	Body mass index
BT	Bacterial translocation
CRP	C-reactive protein
CSA	Cross-sectional area
CV	Coefficient of variation
DUS	Duplex ultrasonography
EN	Enteral nutrition
ERAS	Enhanced recovery after surgery
FAO	Food and Agriculture Organization
FEV_1	Forced expiratory volume after 1 second
FVC	Forced vital capacity
GALT	Gut-associated lymphoid tissue
GP	General practitioner
GSN	Gut-specific nutrient
HAD	Hospital anxiety and depression (score / scale)
ICU	Intensive care unit
IF	Intestinal failure
IP	Intestinal permeability
IGF	Inadequate gut function

IQR	Interquartile range
L:R	Lactulose:rhamnose (ratio)
LREC	Locally organized research ethics committee
MAC	Mid-arm circumference
MLN	Mesenteric lymph node
MODS	Multiple organ dysfunction syndrome
MOF	Multiorgan failure
NG	Nasogastric
NGT	Nasogastric tube
NJ	Nasojejunal
NND	Number needed to diagnose
NNT	Number needed to treat
NPV	Negative predictive value
PEG	Percutaneous endoscopic gastrostomy
PEJ	Percutaneous endoscopic jejunostomy
PEGJ	Percutaneous endoscopic gastrojejunostomy
PICC	Peripherally inserted central cannula
PN	Parenteral nutrition
POSSUM	Physiological and operative severity score for the enumeration of mortality and morbidity (score)
PPV	Positive predictive value
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
SGD	Selective gut decontamination
SMA	Superior mesenteric artery
SOFA	Sequential organ failure assessment (score)
TAMV	Time-average mean velocity
TNF	Tumour necrosis factor
TPN	Total parenteral nutrition
UNU	United Nations University
WHO	World Health Organization

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EXTENDED SUMMARY

Inadequate gut function (IGF) or intestinal failure (IF) is common, particularly in surgical patients and the critically ill. It is difficult to measure objectively, and as a consequence its effects on outcome are contentious and treatment options are limited. Because of the gut's numerous homeostatic functions IF may predispose to delayed sepsis and multiorgan failure (MOF), eventually resulting in death.

The central hypothesis of this thesis was that the state of gut function influences the outcome of patients. As a result, therapies that attenuate gut failure or otherwise enhance the recovery of gut function could possibly improve patient outcomes. This thesis endeavoured to explore this premise by investigating the poorly recognised phenomenon of gut dysfunction and its effect on patient prognosis. Following a review of the relevant literature, the aims of this series of investigations were to assemble the evidence addressing the clinical importance of IF, to define this phenomenon quantitatively, determine its effects, if any, on prognosis and finally to develop a therapy to treat it. These aims were achieved by a series of prospective studies.

Following a literature review, a randomized clinical trial was undertaken in patients undergoing major colonic surgery. This investigated the merits of a multimodal optimization package aimed at enhancing the recovery of gut function when compared to conventional perioperative care. Results showed that implementation of such a

programme curtailed postoperative IF and resulted in an earlier hospital discharge when compared to conventional care. This added support to the contention that IF is clinically important. However, definitive conclusions were limited by the lack of a quantifiable definition for adequate as opposed to inadequate gastrointestinal function. This was addressed in the subsequent series of trials.

It is arguable that the ultimate test of adequate gut function is the ability to tolerate enteral feeding. This idea was pursued in two observational studies which together demonstrated that adequate gut function could be defined quantitatively by the enteral/oral tolerance of at least 80% of calculated nutritional requirements for a minimum continuous period of 48 hours. Anything less than this then represented IGF. This definition was subsequently validated in a separate prospective study in which IGF was shown to be associated with a higher risk of developing sepsis and a poorer prognosis, independently of all other factors that impacted on outcome.

Defining IF in terms of enteral tolerance inevitably poses the question whether the site of feed delivery, be this pre- or postpyloric, impacts on the ability of the gut to tolerate the administered feed. In a trial of 65 patients randomized to receive prepyloric or postpyloric feeding, there was no observed difference in the number of patients in each group that achieved tolerance. Evidence from this work supports the importance of the state of underlying gut function over the significance of the site of feed delivery in the tolerance of an enteral challenge.

The gut may also be studied by assessing splanchnic perfusion and how this changes in response to enteral or parenteral stimulation. Results from this work demonstrated that, as expected, an oral or enteral challenge increased splanchnic perfusion over the fasted state, but in contrast parenteral feed administration resulted in a universal decrease in superior mesenteric artery (SMA) blood flow over preprandial measurements. Further trials are required to establish the therapeutic implications of this observation.

Against this background, an attempt was made to develop a therapy to treat IF based on the use of gut-specific nutrients (GSN) in the critically ill. 50 consecutive patients were randomized to receive a cocktail of GSN (prebiotics, probiotics, glutamine, multivitamins and antioxidants) or placebos. Those involved in the trial were blinded to treatment allocation. The use of GSN was associated with a quicker return of normal gut function, attenuation of the acute phase response, a lower rate of sepsis, and an absolute, albeit not significant, improved survival at three months.

The conclusion from this series of studies was that the state of gut function as defined by the tolerance or otherwise of an enteral challenge, is important to patients as it is independently associated with their prognosis. The site of enteral feed delivery need not overshadow this assessment, but the route of feed delivery impacts on splanchnic perfusion and as such may have therapeutic implications. In addition, much like other single organ dysfunctions, IGF may be targeted by apposite therapies and this resulted in an enhanced recovery of gut function and improved outcomes in critically ill patients. This closed the cause-effect loop relating to the importance of IGF which can now be

defined objectively, measured reproducibly and treated effectively, with resultant benefit to patients. Much like other organ systems, failure of the gut conditions outcome. Apposite therapies to preserve gut function appear to be beneficial and novel strategies to management gut failure need to be developed. Further work is necessary to confirm these findings.

CHAPTER 1:

INTRODUCTION AND LITERATURE REVIEW

"Man and the animals are merely
a passage and channel for food."

Leonardo da Vinci,
1452 -1519 AD

*Excerpts of the literature review in this chapter have been published in an article entitled 'Review article: bacterial translocation in the critically ill - evidence and methods of prevention'. (*Gatt M, Reddy BS, and MacFie J, 2007*).*

1.1 INTRODUCTION

The gastrointestinal tract is a highly complex organ system which has many functions well beyond those of the digestion, absorption and excretion of foodstuffs (Ginsberg and Costoff, 2000; Ganong, 2005). It also acts as a barrier against living organisms and other antigens within its lumen. It periodically samples these luminal antigens to allow for measured immunological responses to be mounted, while simultaneously orchestrating a complex symbiotic relationship with the luminal gastrointestinal microflora. In addition, the gut is also an intricate metabolic, endocrine, exocrine, immunological and cytokine producing organ and is central to a host of other vital homeostatic mechanisms (Figure 1.1).

Given its many roles, it is intuitive that a normally functioning gastrointestinal system is essential to health. A corollary perspective is that inadequate gut function (IGF, syn: gut failure/dysfunction) is deleterious to an individual's outcome. However,

> "traditional teachings…have promoted the dogma that the gut is dormant, metabolically inactive, and of little physiologic and pathologic significance. More recent information has refuted these long-standing beliefs" (Rombeau and Takala, 1997).

The adverse clinical effects of gastrointestinal failure, however, remain to be proven. As such, gastrointestinal dysfunction remains an unrecognised clinical state, there are few if

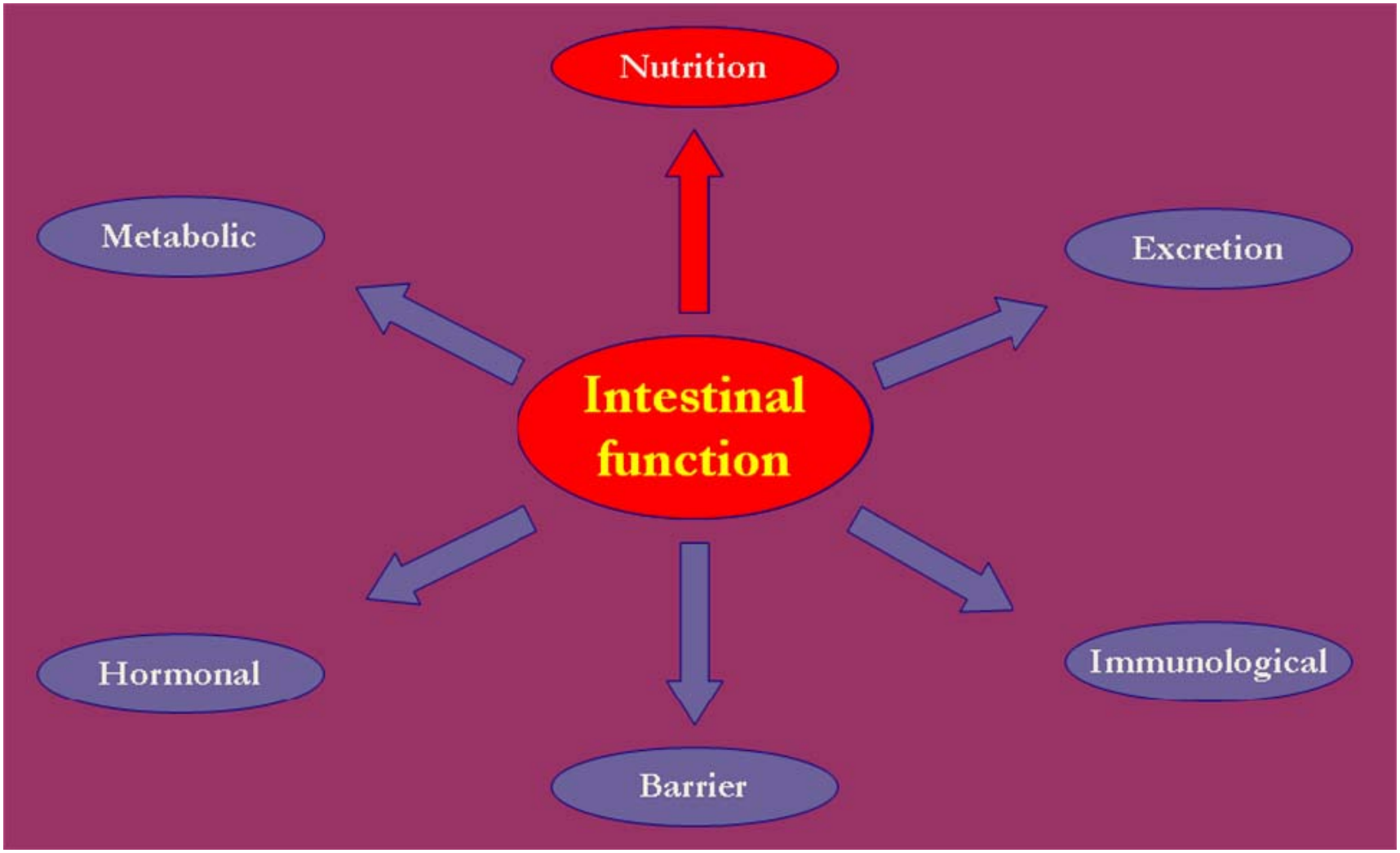


Figure 1.1: The various functions of the gut. The primary function of the alimentary tract is that of nutrition, highlighted in red.

any available treatments for this condition, and consequently it is possible that many patients are being inadequately or inappropriately managed, to their detriment.

Little attention has been given in the literature to the overall functional state of the gastrointestinal tract. This is exemplified by the fact that, unlike other single organ failures which refer to inadequate function of that organ system as a whole, the term 'gut failure' is currently only used in the literature to refer to patients with short gut syndrome or those requiring home parenteral feeding. It must be emphasised that this is not the limited view the author of this work intends when using this term throughout this thesis. In this series of studies, the terms 'gut failure', 'inadequate gut function' and 'gut dysfunction' are used interchangeably to refer to any insufficiency of the gastrointestinal tract mediated by attenuation of its various functions. In this sense, patients with short gut syndrome or those requiring home parenteral feeding are only a small, albeit severely affected, minority. The term is more commonly applicable to the transient attenuation of gut function that is frequently seen in, for example, the immediate postoperative period, the setting of ileus, or that of critical illness, and is more akin to the definition of 'failure' as it applies to other single organs (i.e. inadequate or attenuated function).

There is an abundance of emerging circumstantial evidence which implicates IGF with disease, and in particular, with the onset and propagation of delayed sepsis, MOF, and death. This support for the importance of gut function to patient outcome can be drawn from different (and seemingly unrelated) areas of the medical literature including that pertaining to human nutrition, the gut origin of sepsis hypothesis and enhanced recovery

after surgery (ERAS). The common mechanisms by which gastrointestinal dysfunction cause disease are thought to relate, at least in part, to a disruption of its barrier, immunological and cytokine producing functions. This in turn instigates ingress of micro-organisms and other antigens into the internal milieu in the setting of an otherwise immunocompromised host, resulting in overwhelming sepsis, MOF, and sometimes death (Marshall, Christou and Meakins, 1993; Cohen *et al.,* 2004; MacFie *et al.,* 2006; Gatt, Reddy and MacFie, 2007). The circumstantial evidence supporting the significance of gut failure is discussed in more detail in subsequent sections, however definitive proof for the prognostic importance of gastrointestinal dysfunction remains elusive and provides a justification for the original work presented in this thesis.

1.2 HISTORICAL PERSPECTIVE

The idea that the alimentary tract, teeming with bacteria and other antigens, could represent a source of disease under certain clinical conditions is by no means new. As early as 400 BC, Hippocrates of Kos, the father of modern medicine, is renowned to have said that *'All diseases begin in the gut. Death sits in the bowel; a bad digestion is the root of all evil'* (Bengmark, 2000). In the late 19th century, the idea evolved that peritonitis could result from the passage of bacteria from organs adjacent to the peritoneal cavity. In Germany this was referred to as '*durchwanderungs-peritonitis*', literally translated as 'wandering through peritonitis'. In 1891 and 1895, two separate investigators hypothesized that viable bacteria could pass through the intact gut wall in vivo (Fraenkel,

1891; Flexner, 1895) and in 1900, Ford (1900) managed to culture viable bacteria from the solid organs of human cadavers; organs which were otherwise thought to be sterile. This substantiated theories that it was somehow possible for viable bacteria to gain access to the circulation. Unfortuitously, these and other contemporary findings preceded the development of modern microbiological methods. Inconsistencies in technique made it difficult to draw firm scientific conclusions from such findings and may have hampered a full appreciation of the wide ranging implications of these observations.

It was the classical experiments by Fine and colleagues that appears to have rekindled interest about the role of the gut in the pathogenesis of disease. This work included the successful isolation of viable bacteria from the peritoneal cavity following induction of chemical peritonitis in dogs (Schweinberg, Seligman and Fine, 1950), and a description of the 'bacterial factor in traumatic shock' using a canine haemorrhagic shock model (Jacob *et al.*, 1954; Ravin *et al.*, 1960; Fine, 1965). The importance of maintaining splanchnic perfusion was demonstrated by a study in which the mortality from haemorrhagic shock in dogs was reduced by cross-perfusing the SMA from a second donor dog in order to maintain intestinal blood flow (Lillehei, 1957). As far back as 1955, Schatten, Desprez and Holden (1955) had succeeded in culturing viable bacteria from the portal blood of healthy humans, presumably derived from the gastrointestinal tract. Approximately twenty five years later, descriptive clinical studies identified significant numbers of patients with Gram-negative (Kreger *et al.*, 1980) and enterococcal (Garrison *et al.*, 1982) bacteraemia in whom no primary focus of infection could be found, prompting the suggestion that the gut was probably the source of pathogens in such cases.

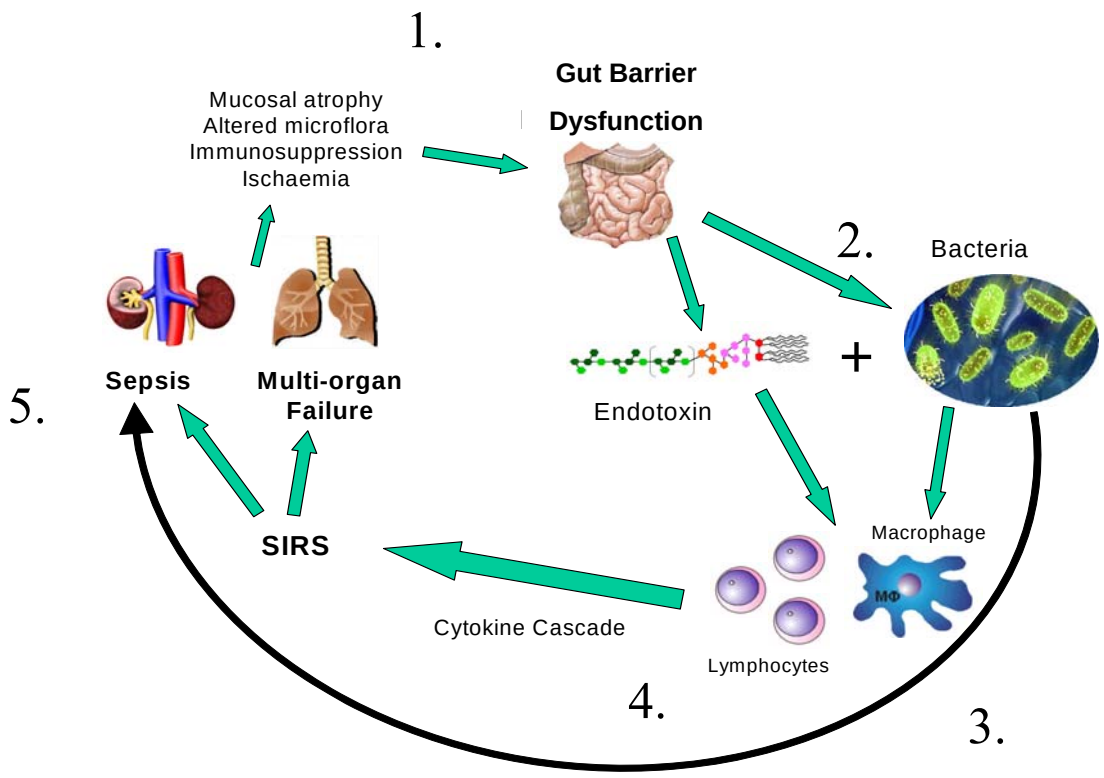
1.3 GUT BARRIER FUNCTION, BACTERIAL TRANSLOCATION AND THE GUT ORIGIN OF SEPSIS HYPOTHESIS

The intestinal epithelium serves as a barrier against living organisms and antigens within its lumen; the so-called 'intestinal barrier function' (Saadia *et al.*, 1990; Deitch, 1993; Adler, 2005; Magnotti and Deitch, 2005;). This gut barrier is still poorly characterised, but is thought to be a highly complex system involving the interplay of a number of physical and immunological components of the gut. A physical barrier is offered by the intact gut mucosa and its tightly controlled intercellular junctions. The production of mucus, numerous secretions that regulate regional gut pH, gastric acid, luminal bile, brush border enzymes, gastrointestinal peristalsis (that controls loco-regional bacterial and antigen counts), the gut-associated lymphoid tissue (GALT), the secretion of luminal immunoglobulins together with the complex regulating properties of resident gut microflora represent but a few additional factors involved in this highly evolved homeostatic mechanism. The fact that luminal contents in the caecum have a bacterial concentration of the order of 10^{12} organisms per ml of faeces (Simon and Gorbach, 1986) whilst portal blood, mesenteric lymph nodes (MLN) and indeed tissues one cell deep to the intact intestinal mucosa are usually sterile, dramatically illustrates the efficacy of this barrier (Baumgart and Dignass, 2002).

The gut's barrier function serves to manage luminal antigens, allows for the safe ingestion of foodstuffs, and encourages the symbiotic relationship between man and enteric bacteria, while constantly ensuring that the internal milieu remains sterile. Breakdown or overwhelming of this barrier may result in the ingress of viable bacteria

and their antigens with the development of sepsis, initiation of a cytokine-mediated systemic inflammatory response syndrome (SIRS), multi-organ failure (MOF), and eventually death. It was Berg and Garlington (1979) who first defined the phenomenon of bacterial translocation (BT) as the passage of viable resident bacteria from the gastrointestinal tract, across the intact mucosa, to normally sterile tissues such as the MLN and other internal organs. The term also applies to the passage of inert particles and other antigenic macromolecules, such as lipopolysaccharide endotoxins and peptidoglicans, across the intestinal mucosal barrier. This role of the gut as 'the motor of multiple organ failure' (Carrico *et al*., 1986; Marshall, Christou and Meakins, 1993; Clark and Coopersmith, 2007) may help to explain the absence of a discreet focus of infection in most patients with delayed SIRS and MOF. The process of gut barrier failure and associated BT describes the gut origin of sepsis hypothesis (Nieuwenhuijzen, Deitch and Goris, 1996; Pastores, Katz and Kvetan, 1996), represented graphically in Figure 1.2.

Whilst it may be tempting to think that any bacteria or endotoxin passing through the intestinal barrier might cause septic complications in the host, there is growing evidence to suggest that translocation may in fact be a normal phenomenon. It is possible that translocation occurs to allow the alimentary tract to be exposed to and sample antigens within the lumen such that the gut can mount a controlled local immune response helping to keep these antigens away from the internal milieu. This process is known as 'oral tolerance' (Song and Whitacre, 2001; Garside, Millington and Smith, 2004; Spahn, andKucharzik, 2004). It is then only when the ingress of micro-organisms and other



KEY

(1). Gut insult such as mucosal atrophy, altered microflora, immunosuppression or ischaemia results in damage to the gut barrier.

(2). This allows bacteria and endotoxin to translocate across the mucosa into the submucosa and reach the gut-associated lymphoid tissues (GALT).

(3). Interaction with macrophages and other immune cells results in the release of inflammatory mediators.

(4). Inflammatory mediators initiate a cytokine cascade which, if uncontrolled, can lead to the systemic inflammatory response syndrome (SIRS).

(5). The combination of uncontrolled systemic inflammation and translocating bacteria reaching the systemic circulation results in end-organ damage.

Figure 1.2: The gut origin of sepsis hypothesis, with BT as a potential stimulus for ongoing inflammation.

antigens is above a critical level, and the host's immune defences are overwhelmed (or otherwise defective) that septic complications arise.

Numerous modifications to the 'gut origin of sepsis hypothesis' have been put forward to attempt to define this process of gut-derived sepsis. Deitch proposed the 'multi-hit model' (Deitch, 2002; Cohen *et al.*, 2004) diagrammatically represented in Figure 1.3. In this model, an initial insult results in splanchnic hypoperfusion (first hit) with the gut becoming a major site of proinflammatory factor production. Resuscitation results in reperfusion which leads to an ischaemia-reperfusion injury to the intestine (second hit) with a resultant loss of gut barrier function and an ensuing enhanced gut inflammatory response, without the need for translocation of microbes as far as the MLN or beyond. Once bacteria or endotoxin cross the mucosal barrier, they can trigger an augmented immune response such that the gut becomes a proinflammatory organ, releasing chemokines, cytokines and other proinflammatory intermediates which affect both the local as well as the systemic immune systems (third hit), finally resulting in SIRS and MOF.

Another modification of the 'gut origin of sepsis hypothesis' is known as the 'gut-lymph theory' (Deitch, 2001; Deitch, Xu and Kaise, 2006) which proposes that macrophages and other immune cells in the submucosal lymphatics of the gut wall or the MLN trap the majority of translocating bacteria. However, those that survive, or the cell wall and protein components of the dead bacteria (including lipopolysaccharides and peptidoglycans) along with the cytokines and chemokines generated in the gut, travel via

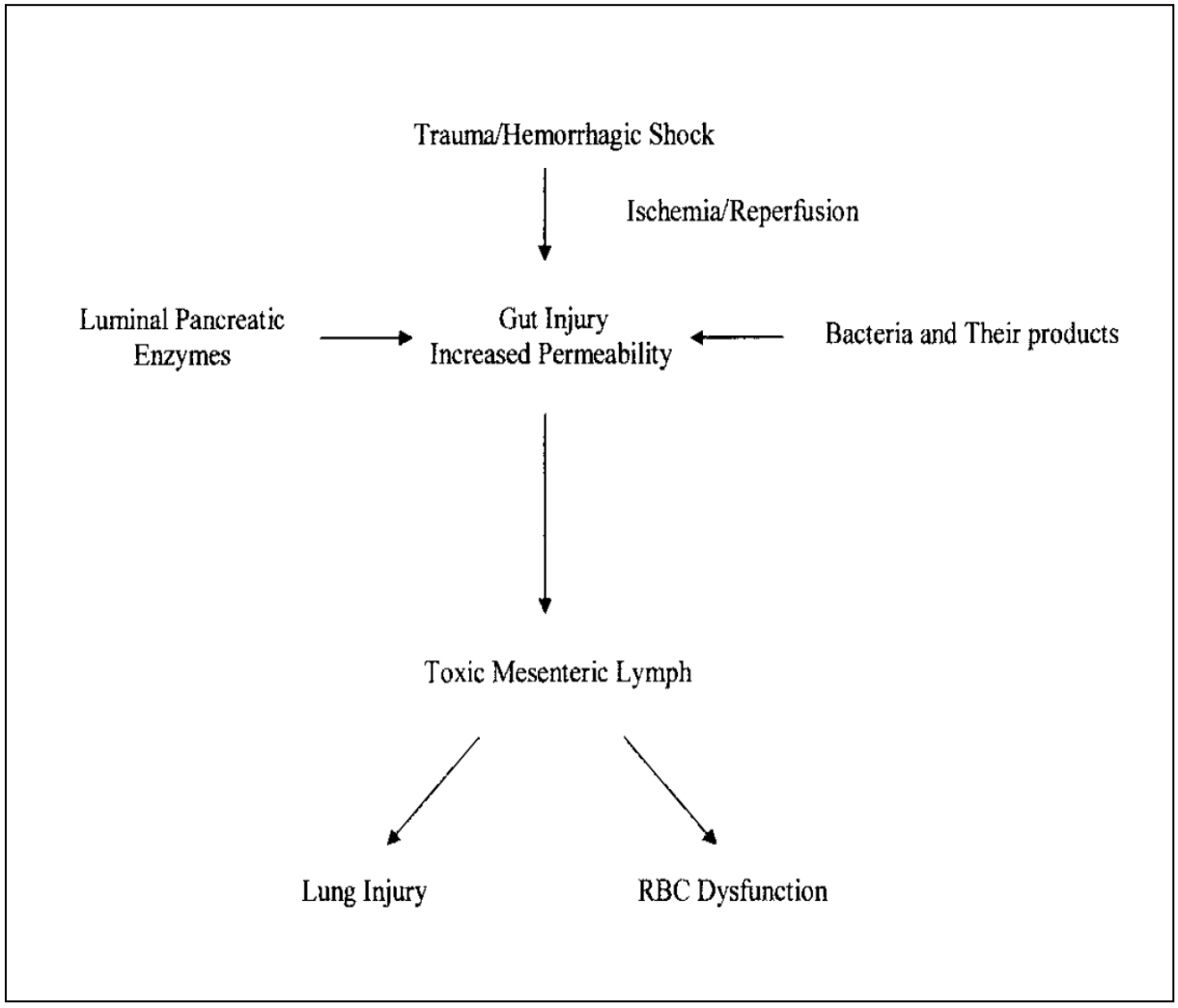


Figure 1.3: The multi-hit hypothesis of distant organ injury following trauma and haemorrhagic shock as proposed by Deitch (Reproduced from Cohen *et al.*, 2004).

the mesenteric lymphatics to the cysterna chilli, and via the thoracic duct empty into the left subclavian vein to reach the right side of the heart. These inflammatory products then enter the pulmonary circulation and activate the alveolar macrophages. In so doing, they contribute to acute lung injury and the progression to adult respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS). This theory corroborates earlier work published by Moore and co-workers who failed to demonstrate bacteria or endotoxins in portal venous blood of polytrauma patients (Moore *et al*., 1991; Koike *et al*., 1994). However, the mechanisms by which translocating bacteria, their antigenic components or cytokines generated in the gut set about causing sepsis and MODS in humans remains unclear.

Luminal bacteria that manage to breach the extrinsic intestinal barrier defences can cross the mucosal epithelium by taking either the transcellular or the paracellular route, or a combination of the two (Wells *et al.*, 1995; Wells and Erlandsen, 1996). On entering the lamina propria, most bacteria are destroyed by macrophages; those that are not, enter the portal venous system and associated solid organs, pass to the MLN, or transgress the peritoneal cavity directly (Figures 1.4 and 1.5). Confirmation of BT therefore necessitates the identification of bacteria in one or more of these sites, making assessments of BT difficult in humans as it necessitates invasive tissue sampling.

The occurrence of BT has been identified in several animal studies. The majority of these studies have involved the culture of MLN to demonstrate BT (Barber *et al.,* 1991; Salman *et al.,* 1992; Kueppers *et al.,* 1993; Shou *et al.,* 1994; Deitch *et al.,* 1995).

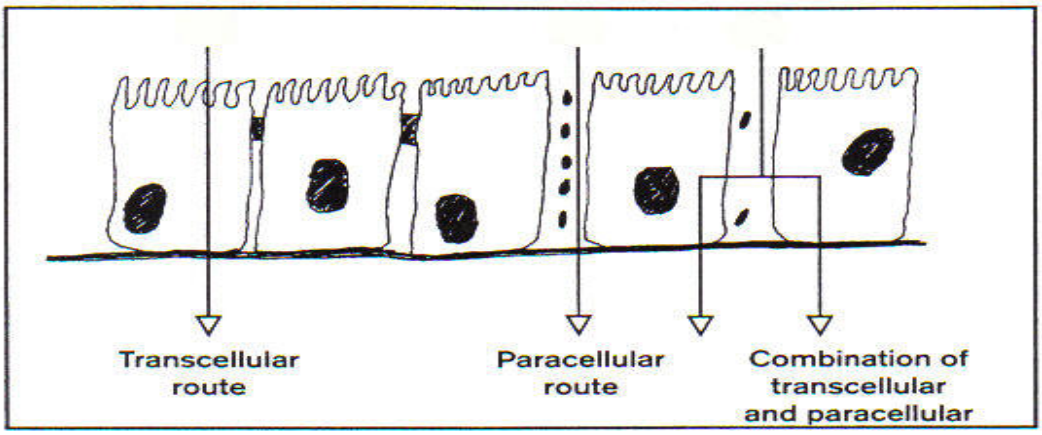


Figure 1.4: Possible routes for BT through the intestinal mucosa

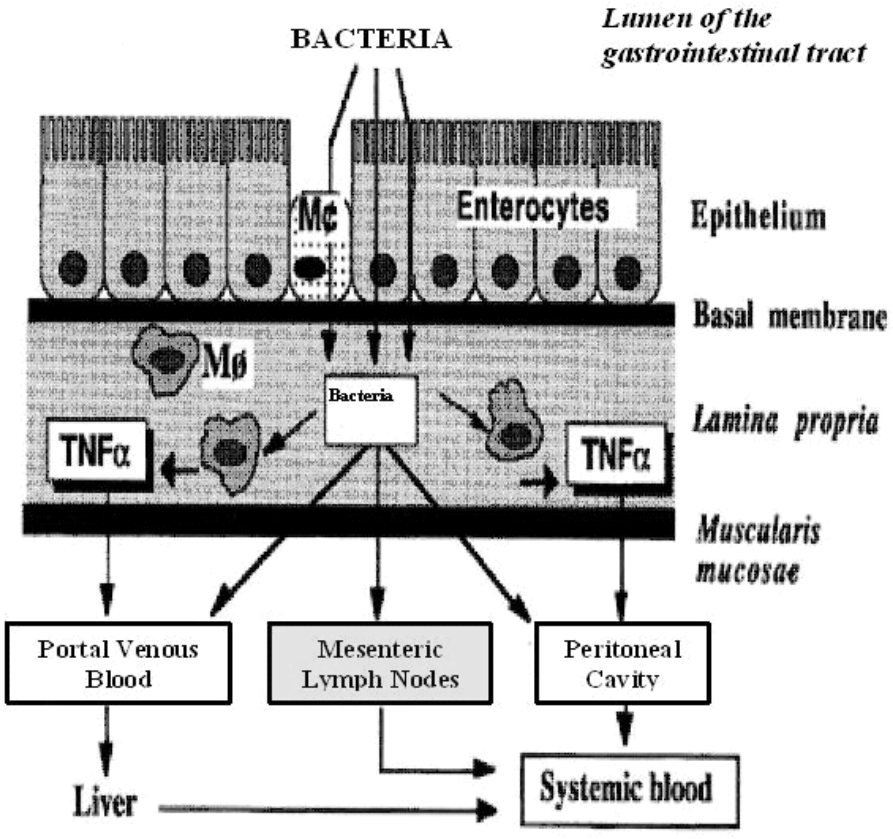


Figure 1.5: Potential sampling sites to assess for BT (figure adapted from open source internet images from www.wikipedia.org).

Using a similar technique, studies in humans have repeatedly demonstrated BT in a wide range of clinical conditions and often associated this with sepsis (Ambrose *et al.,* 1984; Deitch, 1989; Laffineur *et al.* 1992; Sagar *et al.,* 1995; O'Boyle *et al.*, 1998[a]; Sakrak *et al.*, 2003; MacFie *et al.*, 2006).

The process of MLN culture involves the limited sampling of MLN at the time of laparotomy using aseptic techniques, and their subsequent culture on appropriate media (O'Boyle *et al.*, 1998[a]; MacFie *et al.*, 2006). A positive culture is considered to indicate BT. There are a number of limitations to this technique. Firstly, it restricts in-vivo studies relating to BT to surgical patients undergoing laparotomy. Studies investigating BT or barrier function in other clinical conditions have often necessitated extrapolations from animal models. Secondly, there is an ethical and logistical limit to the number of lymph nodes that can be safely sampled in humans. The more extensive sampling possible in animals has resulted in a major disparity in the prevalence of translocation between animal and human studies. BT has been repeatedly reported to occur in approximately 10-15% of surgical patients (Sedman *et al.*, 1994; O'Boyle *et al.*, 1998[a]; MacFie *et al.*, 2006), while some animal studies report a prevalence of greater than 90% (Bai, Jiang and Liu, 1996; Reynolds *et al.*, 1996; Hua and Moochhala, 2000).

The methodological limitations of confirming translocation in humans have major implications to the understanding of this phenomenon; however recent advances in molecular microbiology have opened new frontiers in identifying BT by non-interventional methods. Isolation and sequencing of DNA fragments belonging to enteric

bacteria from peripheral blood and other body fluids may yet permit the confirmation of translocation of enteric organisms without the need for invasive sampling (Kane, Alexander and Johannigman, 1998; Llovet *et al.*, 1998; Wen *et al.*, 2000; Kucukaydin *et al.*, 2000; Hernandez Oliveros *et al.*, 2004; de Madaria *et al.*, 2005; Frances *et al.*, 2005).

A number of factors are thought to influence BT. These are believed to act on the delicate homeostatic equilibrium between luminal organisms and the gut barrier, promoting ingress of antigens across the intestinal barrier (Wells, 1990; Krueger *et al*., 2004). These factors are thought to include intestinal obstruction (Deitch, 1989; Sedman *et al*., 1994; Sagar *et al*., 1995; Kabaroudis *et al*., 2003; MacFie *et al*., 2006), jaundice (Deitch *et al*., 1990[a]; Sedman *et al*., 1994; Kuzu, 1999; Ogata, 2003; Sakrak, 2003; MacFie *et al*., 2006), inflammatory bowel disease (Sedman *et al*., 1994; Takesue *et al.*, 2002; Nazli *et al.*, 2004), malignancy (Lescut *et al.*, 1990; Schoeffel *et al.*, 2000; Takesue *et al.*, 2005), pre-operative total parenteral nutrition (TPN) (Jeejeebhoy, 2001; MacFie *et al*., 2006), emergency surgery (MacFie *et al*., 2006), and gastric colonisation with microorganisms (MacFie *et al*., 1999; MacFie *et al*., 2006). Much of the evidence to substantiate these claims has been derived from animal studies. Further, the number and complexity of factors that interplay at the biome-epithelial interface to bring about translocation makes conclusions regarding factors which are 'independently' important for translocation exceedingly difficult. This is compounded by the fact that most trials investigating translocation have small cohort sizes, permitting only univariate analysis for association.

To date, there is only one published study that investigated factors 'independently' associated with BT in humans. In this study, MacFie *et al.* (2006) performed a multivariate analysis on 927 surgical patients to assess factors independently associated with bacterial ingress across the intestinal barrier. From the large number of variables investigated, and in agreement with previously published literature, intestinal obstruction, jaundice, inflammatory bowel disease, malignancy, pre-operative TPN, and emergency surgery, were all associated with an increased prevalence of BT on univariate analysis. Following multivariate analysis, however, only emergency surgery and pre-operative TPN were shown to be independently associated with translocation (Table 1.1). Even then, the authors were of the opinion that since TPN and gut failure are inextricably linked, and since to date there is no reliable test to identify patients with intestinal failure (IF), the enhanced translocation noticed in this group of patients probably represented little more than underlying gut dysfunction, with TPN representing nothing more than a confounding factor.

Fong *et al.* (1989) showed that healthy volunteers on TPN had a higher tumour necrosis factor (TNF) α, cachectin and C-reactive protein (CRP) levels compared to volunteers on enteral nutrition (EN), suggesting that TPN and bowel rest modify the metabolic response to endotoxins in humans. In addition, animal experiments confirmed that BT occurred more frequently after truncal vagotomy than after proximal gastric vagotomy clearly implying the role of the vagus on gut barrier dysfunction (Doganay *et al.*, 1997). Hasko and co-workers (1998) suggested that the production of TNF α, interleukin 6, 10, 12 and chemokine macrophage inflammatory protein 1α are regulated by transmitters and co-

Factor	No. of patients	Bacterial translocation (%)	p-value univariate	p-value multivariate
All patients	927	130 (14.0)		
Age				
≤70 years	495	60 (12.1)	0.088	
>70 years	432	70 (16.2)		
Sex				
Male	505	62 (12.3)	0.106	
Female	422	68 (16.1)		
Surgery: mode				
Emergency	185	47 (25.4)	**<0.001**	**0.001**
Elective	742	83 (11.2)		
Malignancy				
No	384	61 (15.9)	0.180	
Yes	543	69 (12.7)		
Inf. bowel disease				
No	834	115 (13.8)	0.530	
Yes	93	15 (16.1)		
Jaundice				
No	872	122 (14.0)	0.843	
Yes	55	8 (14.5)		
Preoperative TPN				
No	866	115 (13.3)	**0.021**	**0.015**
Yes	61	15 (24.6)		
Obstruction				
No	788	99 (12.6)		
Gastric Outlet	17	2 (11.8)	0.921	
Small Bowel	77	16 (20.8)	**0.042**	0.895
Large Bowel	45	13 (28.9)	**0.001**	0.246

Table 1.1: Variables independently associated with BT in surgical patients (Reproduced from MacFie *et al.*, 2006).

transmitters of the autonomic nervous system. Brenik *et al.*, (2002) described the parasympathetic regulation of the inflammatory response, 'the cholinergic anti-inflammatory pathway', and demonstrated that efferent vagal nerve stimulation inhibits pro-inflammatory cytokine release and protects against systemic inflammation. There is increasing evidence to suggest that vagal stimulation and cholinergic agonists acting via the 7 α nicotinic acetylcholine (7αn AChR) receptors block endothelial cell activation and leukocyte recruitment during inflammation and improve survival in experimental sepsis (Saeed *et al*., 2005). This substantiates the argument that a functioning gastrointestinal tract is a prerequisite for maintaining the integrity of the immune system and gut barrier function. Since TPN is primarily administered to patients with a non-functioning gut, it is not surprising that it is independently associated with gut barrier dysfunction as measured by BT in surgical patients. It is evident that no matter what mechanisms are involved, the non functioning gut may indeed act as a source of sepsis under certain clinical conditions.

The weight of evidence supports but does not prove the role of BT as a cause of sepsis, as it remains to be proven that the bacteria in MLN actually originated in the gut. However, a recent study by Reddy *et al*. (2007[a]) used PCR and DNA fingerprinting to demonstrate that translocating bacteria in the MLN were genetically identical to those in the faeces. This is, to date, the most compelling evidence supporting the gut origin of sepsis hypothesis, and the pivotal role of the state of gut function in the aetiology of disease. However, similar circumstantial evidence for the importance of gut function can be gleaned from sources other than those investigating BT and the gut origin of sepsis.

1.4 EVIDENCE FOR THE IMPORTANCE OF GUT FUNCTION: NUTRITIONAL STUDIES

Studies relating to the administration of enteral and parenteral nutrition offer added, and potentially more compelling support to the contention that gastrointestinal failure is important to the development of disease. This is particularly true in the postoperative patient and in the settings of trauma and critically illness. As previously mentioned, definitive proof is lacking. In addition, the supporting literature in this respect is overwhelmingly voluminous and precludes an exhaustive review. For this reason, only a few seminal studies will be appraised to exemplify how circumstantial evidence from the field of human nutrition supports the contention that inadequate gastrointestinal function results in poorer outcomes for patients.

Current thinking about nutritional support favours the use of EN over parenteral feeding and the instigation of early enteral alimentation over delayed initiation of EN (ASPEN 2002; Kreymann *et al*., 2006). It is a commonly held belief that feeding into the gut is beneficial to patients, and is associated with improved outcomes, particularly when instituted early, as it is more physiological than TPN. The idea that well nourished patients do better than their malnourished counterparts is well established. However, in a systemic review by Heyland *et al*. published in 2003 which compared early *versus* delayed nutrient intake and their relationship to outcome, the authors reported that early EN was associated with a trend towards decreased mortality and decreased sepsis, even though neither reached significance. Similarly Lewis *et al*. (2001) assessed the merits of

early enteral feeding *versus* 'nil-by-mouth' in patients after gastrointestinal surgery. In this study, Lewis found that early enteral feeding was associated with a decrease in overall sepsis despite an increase in the risk of vomiting. There was also a trend towards decreased mortality with early enteral feeding, but, once again, this did not achieve significance. Finally, a seminal study by Moore *et al*. (1992) investigating 230 patients receiving adjuvant feeding by the enteral or parenteral route, reported that those receiving TPN were more than twice as likely to develop septic morbidity as those patients receiving EN. Results from these and similar studies have been entrenched in European (Kreymann *et al*., 2006), Canadian (Heyland *et al*., 2003) and American (ASPEN 2002) feeding guidelines amongst others. They have also been integrated into nutritional best-practice recommendations of various countries (e.g. National Collaborating Centre for Acute Care, 2006) despite, for the majority, representing grade B evidence or lower. In essence, results from these and similar studies have become part of medical dogma; they establish and shape nutritional practice and many clinicians now accept these recommendations as logical and unshakable truths. These principles promote the use of enteral feeding in preference to parenteral administration, and the use of early enteral feeding over delayed commencement of nutrition.

While there may indeed be some merit in these basic principles, they fail to provide scientific evidence to answer some fundamental questions. These include whether:

- The intravenous administration of nutrients is independently harmful to patients, and if so, why?

- Appropriate TPN administration (i.e. avoidance of overfeeding) independently predisposes patients to sepsis and other complications, and if so, why?

- The lack of nutrition for 24 hours is independently detrimental to patients' outcome (bearing in mind that the difference between early and late instigation of enteral feeding in studies investigating critically ill patients is often considered as being before or after 24 hours from admission to an intensive care setting)?

- The lack of a diet within the lumen of the gut is independently detrimental to the human gut mucosa in the short term as suggested by some animal models?

Convincing scientific answers to these and other pertinent issues do not exist in the published literature. This raises doubts about the *prima facie* evidence presented by the basic nutritional principles previously mentioned. As such, it may be justifiable to ask what these and other nutritional studies, as a collective, are actually demonstrating. Are they really suggesting that the timing and route of feed administration are of crucial prognostic significance? Are these studies suggesting that the intravenous administration of nutrients is positively harmful to patients as this predisposes them to sepsis and possibly death? Or is it just possible that it is actually underlying gut function which is important, as it is this that then conditions the timing and method of patient feeding? Is it conceivable that if a patient's gut does not work adequately (such that the patient necessitates parenteral nutrition), then any predisposition to septic complications arises

by virtue of the fact that the patient has impaired gut immunological function and not as a direct result of the intravenous administration of nutrients? Indeed is it plausible that these papers are highlighting the importance of epiphenomena (i.e.: TPN and delayed enteral feeding causing sepsis, MOF and death) while ignoring the event actually responsible for the observed differences, that of gut dysfunction? Is it therefore time for a new paradigm with regards to nutritional studies, one that considers the underlying state of gut function as being of paramount importance, and not the timing or method of feeding?

Unfortunately the literature is very sparse in this area, not least because it is ethically questionable to perform clinical trials where patients are randomized to either enteral or parenteral feeding without some consideration for their underlying gastrointestinal function. However, there is at least one such study in the literature where this problem was overcome by means of an ingenious study design. This study by Woodcock *et al*. (2001) was originally set up to compare enteral and parenteral feeding. However, the final conclusions of this study, possibly more than those of any other single trial, support the idea that the state of gut function is central to health and disease. To appreciate the importance of this study, it is necessary to understand the intricacies of its design (Figure 1.6). This study will be discussed in detail, not only because it represents a cornerstone in nutritional research, but more so because the findings of this study led to the ideas and hypothesis which brought about this thesis.

This trial by Woodcock *et al*. (2001) was a prospective study of 562 patients requiring

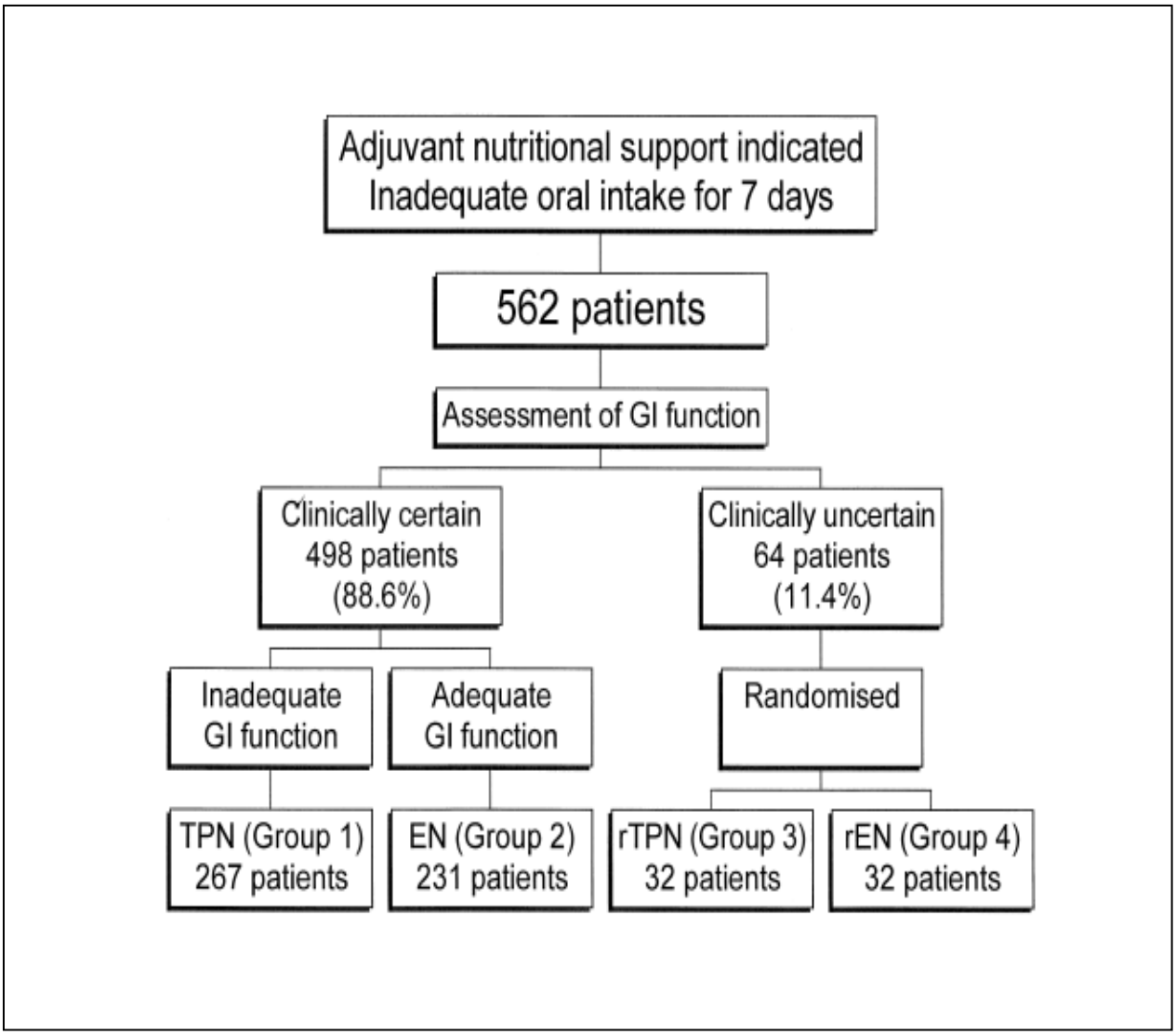


Figure 1.6: Flow diagram of the study design (reproduced from Woodcock *et al.,* 2001). EN, enteral nutrition; rEN, randomized EN; TPN, total parenteral nutrition; rTPN, randomized TPN.

adjuvant nutritional support in which patients were allocated to one of four groups for purposes of feeding. In the first and most crucial step of patient allocation, clinicians were asked to assess the patients' gastrointestinal function clinically. Patients were then assigned to one of two main arms of the study, either those in whom the clinicians were 'certain' of what the gut was doing, or those in whom they were 'uncertain'. Those patients in whom the clinicians were certain of the state of underlying gut function were then fed accordingly; patients deemed to have a normally functioning gut were fed enterally (group 1), while those with IGF were fed using TPN (group 2). On the other hand, those patients who had dubious gastrointestinal function were randomized to receive either EN (group 3) or TPN (group 4). This original design allowed investigators to overcome the ethical dilemma of randomization encountered in similar nutritional studies.

The results of this study showed that with regard to the adequacy or inadequacy of feeding (inadequate feeding was defined as the delivery of less than 80% of prescribed feeds) a significantly higher proportion of patients receiving EN were underfed when compared to their counterparts receiving TPN (Figure 1.7). Over 30% of patients in Group 1 were inadequately fed. This difference was even more marked in the randomized groups where more than 60 % of patients randomized to receive EN received inadequate intakes.

As regards non-septic morbidity, patients fed enterally had more delivery system related complications, as well as feed-related morbidity, than their TPN counterparts

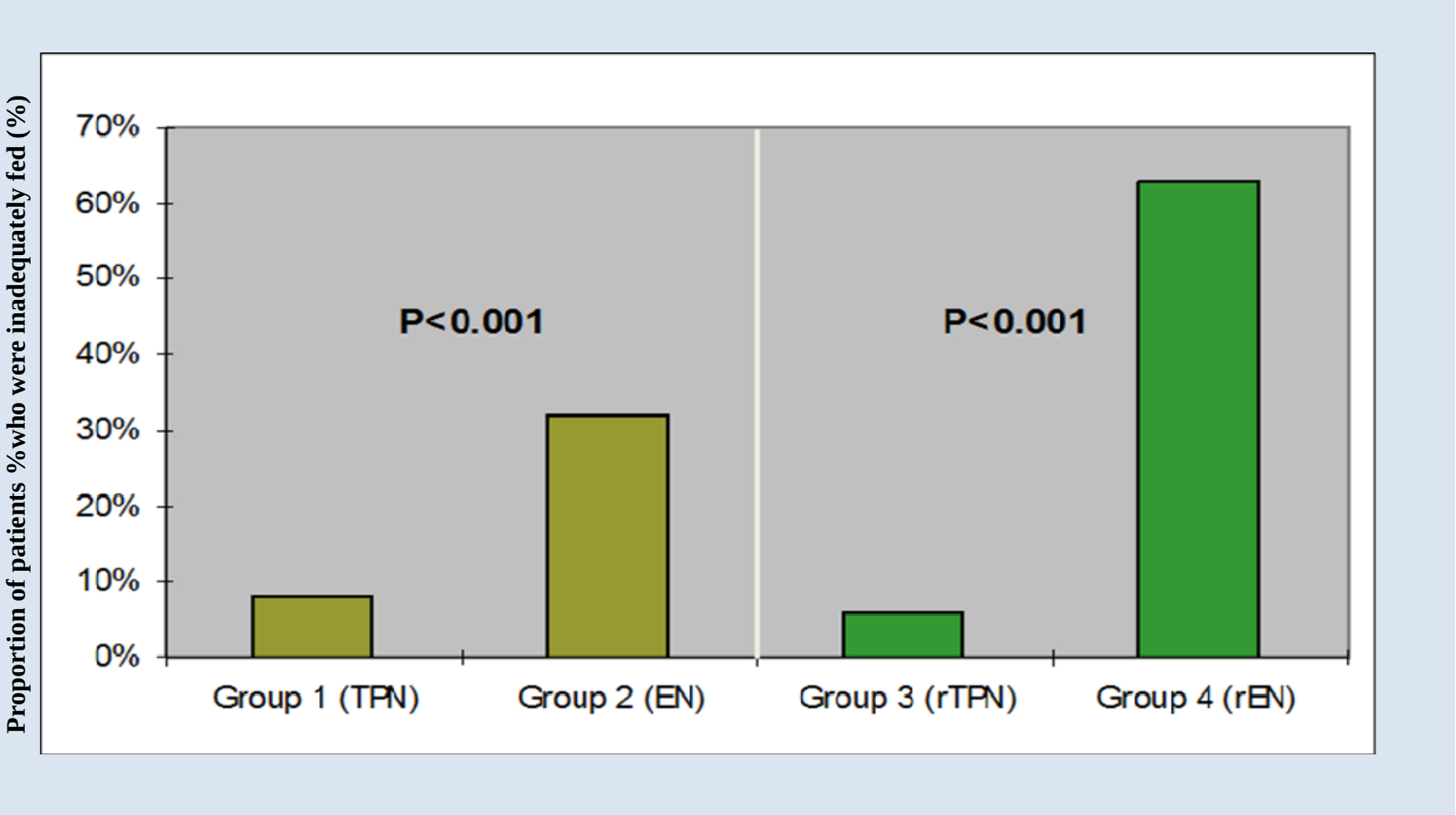


Figure 1.7: Inadequacy of feeding in the various groups where inadequate feeding was described as <80% of nutritional requirements (adapted from Woodcock *et al.,* 2001). EN, enteral nutrition; rEN, randomized EN; TPN, total parenteral nutrition; rTPN, randomized TPN.

(Figure 1.8). However, with reference to septic morbidity, the investigators reported no differences between patients fed enterally and those fed parenterally (Figure 1.9). In contradistinction to the majority of observational studies in the literature at the time, patients receiving EN in this study had a higher absolute mortality than patients assigned to TPN feeding, irrespective of whether they had been clinically assigned to this feeding modality or had been randomized to EN (Figure 1.10). This difference was significant in the clinically assigned groups but not in the randomized cohorts.

Taking all these results together, many have interpreted this study as definitive proof that TPN is, contrary to popular belief, better in many ways than EN. TPN allowed for more adequate feeding, resulted in less non-septic complications and ultimately was associated with a lower mortality. This argument may be valid if one believes that the route of administration of feeds has a bearing on outcome. However, enteral feeding is more physiological than TPN as it makes use of the gut and therefore, theoretically at least, should be associated with better or equivalent outcomes, not worse.

There is, however, a second more intriguing interpretation of these results that the authors allude to in their conclusion. In their words, they state that…

> "If adequate volumes (*of feed*) are tolerated then TPN is clearly not required and the absence of intestinal failure is probably a favourable prognostic indicator." (Woodcock *et al.,* 2001)

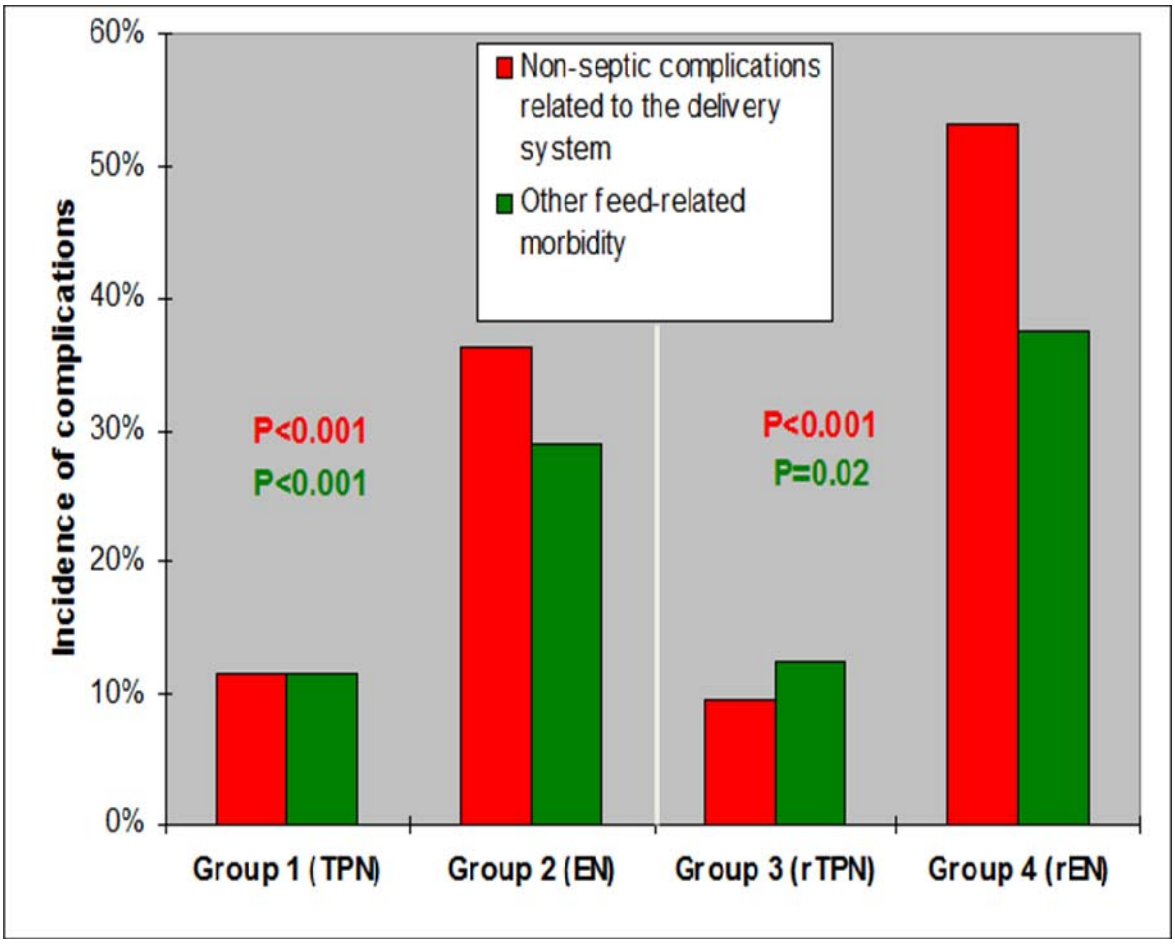


Figure 1.8: Non-septic complications in the various groups (adapted from Woodcock *et al.*, 2001). EN, enteral nutrition; rEN, randomized EN; TPN, total parenteral nutrition; rTPN, randomized TPN.

INCIDENCE OF SEPTIC MORBIDITY

	Nonrandomized patients		
	Group 1 (TPN)	Group 2 (EN)	*P* value
Incidence of septic complications	84/267 (31.5%)	81/231 (35.1%)	0.48, NS
Mean no. of complications per patient (± SEM)	0.44 ± 0.05	0.45 ± 0.05	>0.05, NS
Mean no. of complications per infected patient (± SEM)	1.40 ± 0.07	1.30 ± 0.07	>0.05, NS
	Randomized patients		
	Group 3 (rTPN)	Group 4 (rEN)	*P* value
Incidence of septic complications	16/32 (50%)	10/32 (31.3%)	0.13, NS
Mean no. of complications per patient (± SEM)	0.75 ± 0.16	0.41 ± 0.12	>0.05, NS
Mean no. of complications per infected patient (± SEM)	1.50 ± 0.16	1.30 ± 0.15	>0.05, NS

Figure 1.9: Septic complications in the various groups (reproduced from Woodcock *et al.,* 2001). EN, enteral nutrition; rEN, randomized EN; TPN, total parenteral nutrition; rTPN, randomized TPN; SEM, standard error of mean.

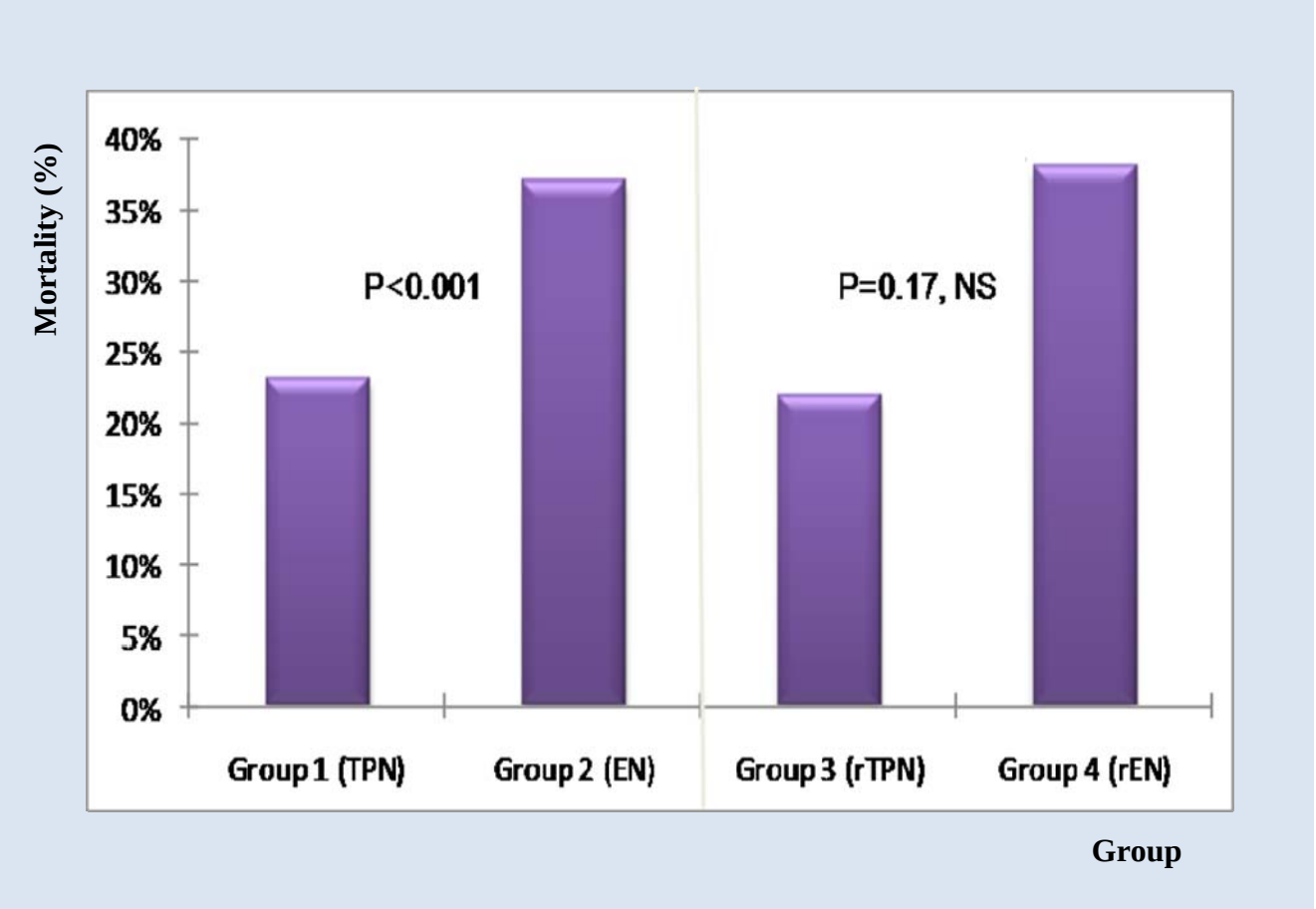


Figure 1.10: Mortality in the various groups (adapted from Woodcock *et al.*, 2001). EN, enteral nutrition; rEN, randomized EN; TPN, total parenteral nutrition; rTPN, randomized TPN.

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Considering that the original assignment to groups in this study was left to clinicians to make on clinical grounds, the findings of this study may be suggesting a more subtle truth, namely that doctors are poor at assessing the adequacy (or otherwise) of gut function clinically. This is all the more plausible given that there is currently no validated, objective and quantifiable definition for normal as opposed to abnormal gut function (Rombeau and Takala, 1997). The fact that 32 per cent of patients clinically assigned to receive enteral feeding in the Woodcock study (on the assumption that their gut was working) in fact failed to tolerate even 80% of their nutritional requirements (Woodcock *et al*., 2001) seems to support this contention. In other words, many patients deemed to have a normally functioning gut actually had a gut with attenuated function that did not permit adequate tolerance of nutrition. These findings therefore suggest that poor gut function (resulting in inadequate intakes in patients assigned to EN) was associated with poorer outcomes. That is to say, it is underlying and often unrecognized gut failure not the route of feeding (be that EN or TPN) that conditions outcome.

There are some, albeit few studies in the literature to corroborate this interpretation of the results from the Woodcock study. One such trial by Raff, Hartmann and Germann (1997) investigated 55 burns patients. In this study, patients were subdivided into two groups; these who were able to achieve tolerance of their nutritional goals in less than 72 hours and those that required longer than 72 hours (Figure 1.11). These two groups were comparable in most respects, including their degree of burns as assessed by the abbreviated burn severity index. However, mortality differed significantly between the two groups. Raff and co-workers noticed that those patients achieving tolerance in less

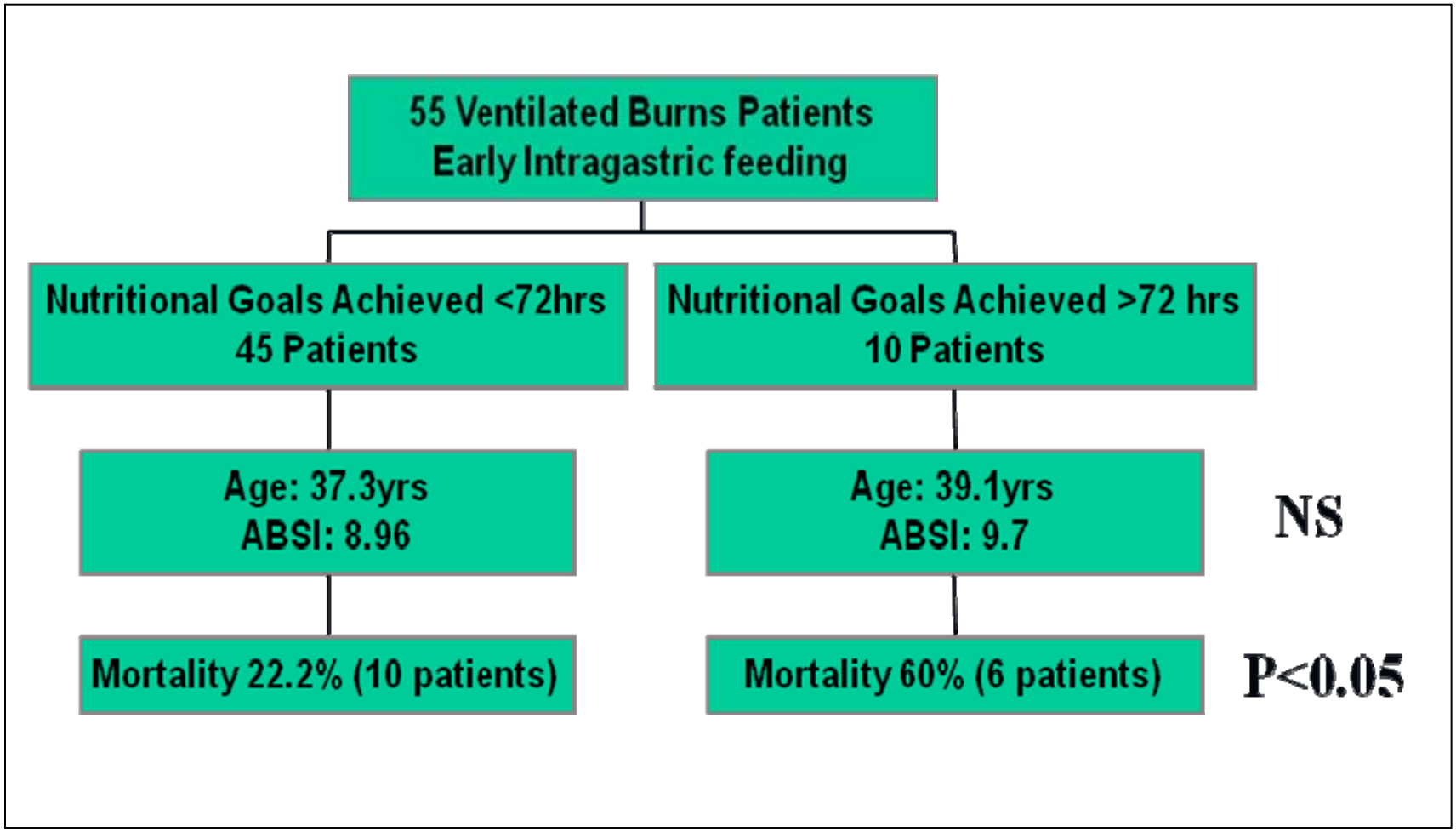


Figure 1.11: Study design (adapted from Raff *et al*., 1997).

than 72 hours had a mortality of 22%, while those that took longer than 72 hours to achieve feed tolerance had a significantly higher mortality of 60% ($p<0.050$) . These results again suggest that the state of underlying gut function, and the ensuing tolerance or intolerance of feeds administered to the gut, has a prognostic significance.

1.5 EVIDENCE FOR THE IMPORTANCE OF GUT FUNCTION: STUDIES RELATING TO ENHANCED RECOVERY AFTER SURGERY

Further evidence for the importance of the gut in conditioning patients' outcome may be gleaned from trials investigating so called 'fast-track' programmes of perioperative care. These management protocols, otherwise called enhanced recovery after surgery (ERAS) programmes or multimodal optimization (MMO) packages, involve a number of treatment strategies aimed at optimizing perioperative care (Figure 1.12; adapted from Fearon *et al.,* 2005). Studies of this nature have repeatedly been shown to result in improved post-operative outcomes in patients undergoing elective surgery (particularly colorectal surgery) by reducing morbidity, expediting recovery and curtailing hospital stays in the optimized groups (Anderson *et al*., 2003; Kehlet and Wilmore, 2005; Fearon *et al.,* 2005; Wind *et al*., 2006).

Benefits of such fast-track programmes have been attributed to a reduction in the stress response to surgery. The 'surgical stress response' however is a rather vague and poorly defined entity, and as such the underlying mechanisms that bring about these improved

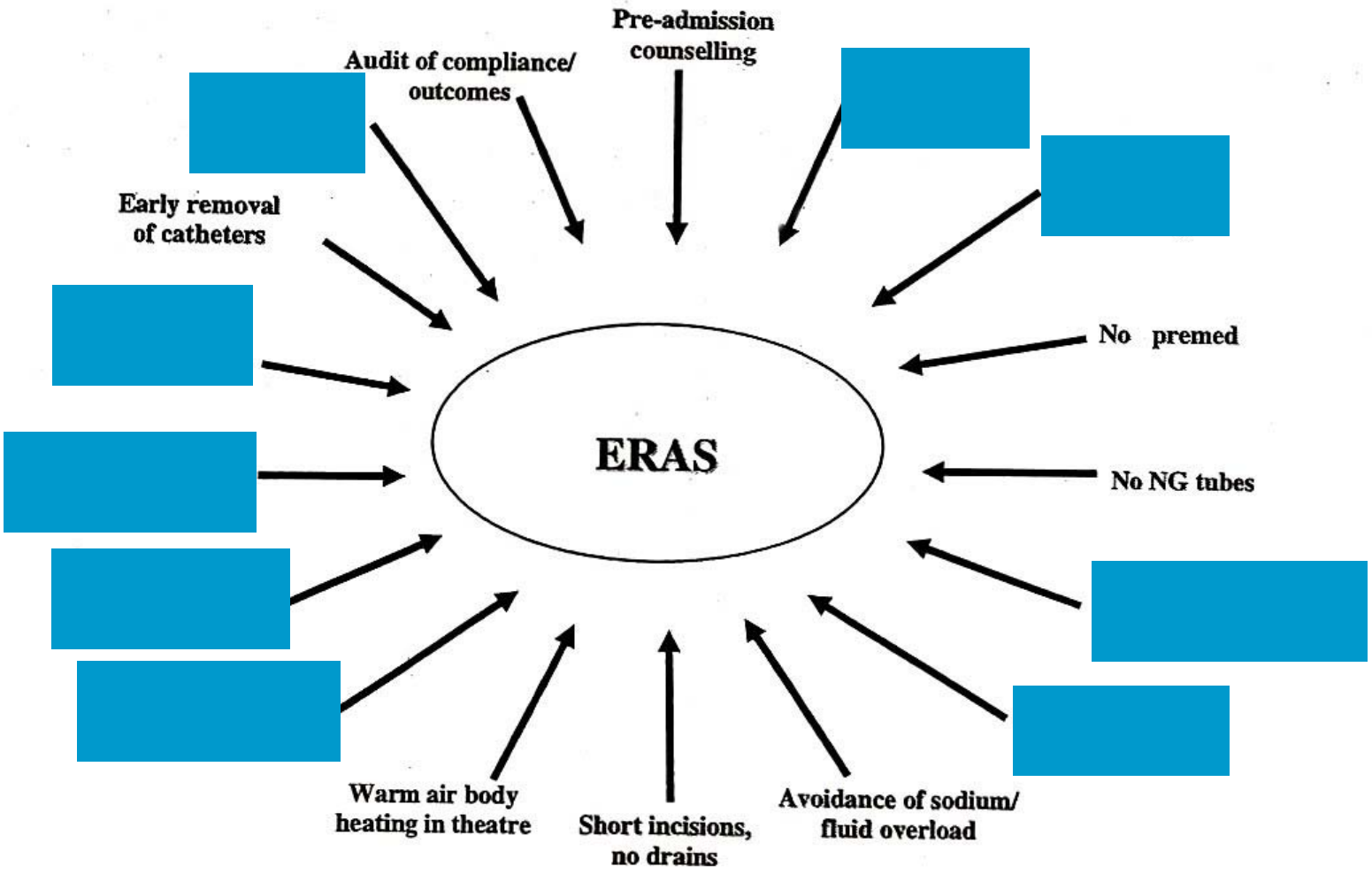


Figure 1.12: Strategies that may enhance recovery after surgery (adapted from Fearon *et al.*, 2005). Strategies in blue act on the gut.

outcomes are, at best, poorly characterised. The stress response is thought to be mediated via neuroendocrine mechanisms leading to alterations in protein homeostasis (increased catabolism), hypermetabolism, altered carbohydrate metabolism (increased gluconeogenesis and insulin resistance) and increased lipolysis (Weissman, 1990; Desborough, 2000; Holte, Sharrock and Kehlet, 2002). In the short term, the stress response can be advantageous, but over a longer period it can lead to organ dysfunction, loss of lean body mass, reduced muscle power, and fatigue (Henriksen, 2000). Optimization packages are thought to work by preserving postoperative organ function, including the attenuation of transient postoperative cardiac, respiratory and renal failure (Kehlet and Wilmore, 2005). It has also been suggested that the earlier return of normal gut function, noticed by some investigators, is pivotal in bringing about the benefits of multimodal optimisation (Gatt *et al*., 2005, Wind *et al*., 2006).

This understanding is based on a number of observations. Firstly, optimization is associated with an earlier tolerance of food (Anderson *et al*., 2003, Gatt *et al*., 2005), curtailed postoperative ileus, and a lower prevalence of postoperative nausea and vomiting (Kehlet and Dahl, 2003). Secondly, many of the treatment strategies included in optimization packages, such as early mobilisation, synbiotics, opiate avoidance, use of epidurals, high inspired oxygen concentrations, and early enteral challenge, primarily affect the gut (Figure 1.12). Thirdly, the gastrointestinal system with its GALT constitutes more than 50 percent of the body's immunological cell mass and plays a central role in orchestrating the stress response to surgery. GALT is only one aspect of intestinal barrier function and maintenance of normal nutrition may prevent its

breakdown (DeWitt and Kudsk, 1999).

The exact mechanisms responsible for the improvements in outcome noted with optimization of care remain unclear. Enhanced recover could, in part, be due to improvements in the return of gut function, but this cannot be ascertained from the published literature because of the difficulties (and the lack of standardization) when assessing gut function (Elia, Stroud and Itobi, 2006). Once again this emphasises the need for an objective definition of what constitutes 'adequate' as opposed to 'inadequate' gut function.

1.6 DEFINING GUT FUNCTION AND FAILURE: BASIC CONCEPTS AND CONSIDERATIONS

There is currently neither an accepted objective and quantifiable definition for what constitutes adequate gut function, nor, in its absence, the state of gut dysfunction. For this reason, it is not clinically possible to accurately and reproducibly identify those patients who have a normally functioning gastrointestinal tract as distinct from those whose gut is failing. Clinicians still resort to the use of traditional surrogate markers of gut function such as the auscultation of bowel sounds, the passage of flatus and faeces or the tolerance of an unquantified enteral challenge (Rombeau and Takala, 1997, Seidner and Ramasamy, 2005). These observations are all somewhat subjective and have long been known to be of limited clinical value in assessing underlying gut function (Baker and

Dudley, 1961; Rothnie, Harper and Catchpole, 1963). As a direct result, the clinical importance of the state of gut function is immeasurable and remains unknown, despite the wealth of circumstantial evidence linking the gut to the development of delayed sepsis, MOF and death. In addition, the absence of a definition makes it impossible to develop validated therapies aimed at attenuating the period of gut dysfunction or to treat patients with established gut failure. There is currently no yardstick against which to measure the effects of such therapies.

One of the difficulties in establishing a definition for gut function or failure is that, unlike other single organs (e.g. the heart, lungs and kidneys), the gut is functionally much more complex, being involved in a multitude of metabolic processes (Figure 1.1). Numerous tests have been described to assess isolated aspects of gastrointestinal function including investigations which assess intestinal anatomy and length, intestinal motility, splanchnic flow, gut absorption and permeability, nutritional status, gastrointestinal hormone production, as well as barrier and immunological function. Table 1.2 provides a non-exhaustive list of these tests. To date, there are, however, no tests that assess 'overall' gastrointestinal function in a way which can be easily applicable clinically.

Developing a definition to characterise the state of gut function or failure, which would also relate to outcome, be objective, quantifiable, reproducible and clinically applicable would undoubtedly prove challenging. One possible approach would be to model such a definition on concepts which govern how the funtion of other organs is defined. In broad

CATEGORY	TEST		
Gastrointestinal anatomy, length and perfusion	**Radiology** - Contrast meal ± opisometer - Contrast enema - Fistulogram - Ultrasound - CT scan - MRI	**Peroperative intestinal length evaluation**	**Studies of gastrointestinal perfusion** - Doppler ultrasound flowmetry - Gastrointestinal tonometry - Plasma indocyanine green clearance - Reflectance spectrophotometry - Portal vein catheterization - Angiography
Gastrointestinal motility	**Transit studies** - Scintigraphy - Ultrasonography - Bioelectrical impedance - MRI - Acetoaminophen absorption - ^{14}C octanoic acid breath test - Hydrogen breath test - Sulphasalazine absorption assay - Gastric residual volume assessment - Phenol red / polyethylene dilution	**Assessment of contractile activity** - Catheter manometry - Barostat assessment **Assessment of electrical activity** - Surface electrogastrography - Intraluminal electromyography	**Studies of gastrointestinal reflux** - Continuous pH monitoring - Intraluminal electrical impedance - Bilitec 2000 - Exogenous isotopic marker studies

CATEGORY	TEST		
Gut digestion, absorption and permeability	**Urine** - 24 h urinary electrolytes & nitrogen - Dual sugar intestinal permeability - Triple sugar intestinal permeability - D-xylose absorption **Blood** - Serum biochemistry - Postprandial plasma citrulline - Pancreolaural test - Secretin-pancreozymin - Serum carotene	**Stools** - Gross inspection - Stool microscopy - 24 hour stool fat & protein content - 5 day stool fat balance - Radiolabeled albumin / caeruloplasmin assays	**Other** - ^{14} C-triolein breath test - ^{13} C-Trioctanion test - Hydrogen breath test - Schilling test - Tracer studies for iron, calcium, amino acids, vitamins etc - 75 SeHCAT bile malabsorption test - Mucosal biopsies
Gut barrier and immunological function	**Bacterial translocation** - Mesenteric lymph node culture - Blood PCR for bacterial fragments	**Mucosal biopsy** - Villous height & morphology - Assessment for lymphocyte counts	**Intestinal permeability assays**

CATEGORY	TEST		
Nutritional status	**Anthropometry** - Weight & height - Unintentional weight loss - BMI - Mid-arm circumference - Skin fold thickness **Blood** - CRP - Serum albumin & prealbumin - Serum cholesterol - Essential fatty acid profile	**Clinical** - History taking - Food diary - Grip strength - Spirometry - Scoring systems (prognostic nutritional index subjective global assessment, etc.) - Malnutrition universal screening tool (MUST)	**Body composition measurements** - Isotope dilutional tests - Bioelectrical impedance - Dual energy X-ray absorptiometry - CT scan - MRI - Whole body counting / neutron activation **Other** - Creatinine–height index - Delayed cutaneous hypersensitivity
Gastrointestinal hormone production	**Serum hormone assessments** - Various		

Table 1.2: Tests for the various functions of the gastrointestinal tract.

terms, for example, cardiac function is defined by indices of cardiac output and end organ perfusion, respiratory function by relating this to ventilation, oxygenation and carbon dioxide clearance, and renal function in terms of the adequacy of urine output, glomerular filtration rate and creatinine clearance values. The attenuation or absence of normal function then implies organ failure.

All these single organs have secondary or subsidiary functions. The kidneys, to take one example, are also involved in the renin-angiotensin system and in haematopoesis but these and other ancillary functions are not normally considered when defining normal renal function. Renal function or failure is determined by its role as an organ of excretion. Consequently, it is apparent that the function of an organ is described in relation to the primary role of that organ, to the exclusion of its supplementary functions.

This becomes particularly relevant to the definition of normal gastrointestinal function when one considers the plethora of functions of the gastrointestinal tract (Figure 1.1). Despite a multitude of metabolic functions, the primary role of the gut remains that of nutrition. In common with other organ systems, its state of function or failure should therefore, theoretically at least, be defined in terms of this, its primary role. Extrapolating this idea further, an all inclusive definition to take into consideration all aspects of gut function is not possible, probably unnecessary, and conceptually wrong. This does not happen for other single organs, and in the same way is probably also unnecessary for defining gut function.

The clinical complexities associated with, for example, cardiac, respiratory, and renal failures have resulted in numerous definitions for what constitutes normal organ function and what constitutes organ failure. The specific clinical setting then determines which definition is most applicable. No definition is all-inclusive or universally applicable. This would also be expected to hold true for the definition of gut function and failure. Any definition will, by default, have limitations to its uses and applicability. With this conceptual background, it would be desirable for an appropriate definition that distinguishes adequate from IGF to:

- relate to the primary function of the gut.
- be objective.
- be discriminative.
- be quantifiable (to permit reproducible measurements).

Other desirable properties of such a definition include:

- clinical applicability.
- an evidence-base.
- an association with patient outcome.

The possibility of incorporating indicators of severity (e.g. mild, moderate or severe) and periodicity (e.g. acute or chronic) into the definition has also been suggested (Nightingale, 2001; O'Keefe *et al*., 2006).

There have been numerous attempts at characterising the state of gut function but none have been easily applicable clinically or widely accepted. The term 'intestinal failure' was first used by Milewski *et al*. (1980) in their paper entitled 'Parenteral nutrition at home in management of intestinal failure'. A year later, Fleming and Remington formulated what is commonly considered to be the first definition of this phenomenon as:

> "...a reduction in functioning gut mass below the minimal amount necessary for adequate digestion and absorption of nutrients." (Fleming and Remington, 1981)

From this early stage it became apparent that despite the many functions of the gastrointestinal system, the over-riding principle of defining the performance of an organ based on its primary role was being observed. It is clear that the primary role of the gut is one of nutrition, and its state of function or failure should be defined as such. All subsequent attempts at establishing a definition have also kept to this central concept. It took another 20 years until a second attempt was made at defining IF. In his book by the same title published in 2001, Nightingale established that:

> "Intestinal failure occurs when there is reduced intestinal absorption so that macronutrients and/or water and electrolyte supplements are needed to maintain health and/or growth. Undernutrition and/or dehydration result if no treatment is given or if compensatory mechanisms do not occur." (Nightingale, 2001)

Nightingale (2001) further attempted to develop both a classification (acute or chronic), as well as a severity grading of gut failure (mild, moderate and severe). He also recognised that severity of IF represented a continuum on which patients could move up or down dependent on factors such as compensatory mechanisms, drug therapy, or progression of underlying disease states. This also initiated the idea that IF was potentially amenable to modulation and therefore treatment.

A more recent, albeit analogous definition for IF was drawn up by a consensus group who proposed that:

> "Intestinal failure results from obstruction, dysmotility, surgical resection, congenital defect, or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance" (O'Keefe *et al*., 2006).

This same consensus group formulated a novel taxonomy to incorporate both the temporal as well as the severity classification first drawn up by Nightingale. However, the simplest but possibly the broadest definition of gut failure was formulated by Khursheed Jeejeebhoy who characterises IF to occur when...

> "...gastrointestinal function is inadequate to maintain the nutrition and hydration of the individual without supplements given orally or intravenously." (Jeejeebhoy, 2005)

This author continued by qualifying that "...major resection ... can cause severe malabsorption and effectively behave clinically like 'intestinal failure' (but) without loss of intestinal function." This suggests that IF relates more to a loss of gastrointestinal function than simply to a loss of structure (i.e. bowel length).

What becomes immediately apparent from these and other definitions is that, while they all characterise gut function or failure in terms of its nutritional capacity, they stop short of quantifying the condition of IF in such a way that permits prompt recognition by the bedside in an objective and reproducible fashion. For these and other reasons, and despite the availability of established definitions, clinicians still feel it necessary to use a number of surrogates to indicate and monitor the adequacy (or otherwise) of gut function. These include the auscultation of bowel sounds and the passage of flatus or faeces. However, these and other indicators have long been shown to bear little clinical significance to outcome (Baker and Dudley, 1961; Rothnie, Harper and Catchpole, 1963) particularly because of their subjectivity and irreproducibility.

One indicator which may still bear some clinical potential is that of tolerance to an oral or enteral diet, the concept of 'enteral tolerance'. In a statement from a conference set up to discuss gut dysfunction in critical illness, the panel of experts concluded that:

> "Due to the lack of objective, uniform definitions of gut dysfunction, monitoring of gut function must be based on indirect indicators. Tolerance to enteral feeding is probably the most commonly used

> indicator in the clinical setting. Its relevance can be improved when performed in the context of a predefined feeding protocol. ... Intolerance to an appropriate regimen of enteral nutrition is probably the most practical finding at the bedside. Despite obvious limitations to this definition, it provides a functional assessment with some clinical relevance. A more objective definition of intestinal dysfunction will undoubtedly emanate in the future…". (Rombeau and Takala, 1997)

Taking this lead, this indicator of tolerance by the gut to an orally or enterally administered challenge will be investigated in detail throughout this thesis in an attempt to derive a more objective and clinically applicable definition to indicate the state of gut function. Against this background, one possible way of defining gastrointestinal function in terms of enteral tolerance might be to define adequate gut function by:

> 'The tolerance of adequate oral or enteral intake to satisfy basic nutritional requirements.'

Anything less than this would then, by inference, represent gut failure as a result of inadequate function. Such a description takes into consideration some, but not all, of the desirable criteria for a satisfactory definition set out above (section 1.6). However, while

being a plausible characterization, it lacks objectivity and reproducibility because of the absence of quantifiable terms.

Basic nutritional requirements can be established by means of indirect calorimetry (which assesses energy expenditure) or the use of apposite validated models such as the Fleisch, Harris-Benedict, Schofield, Schebendach or, Food and Agriculture Organization / World Health Organization / United Nations University (FAO/WHO/UNU) equations (Harris and Benedict, 1919; Kleiber, 1932; Fleisch, 1951; Robertson and Reid, 1952; Kinney *et al*., 1964; World Health Organization, 1985; Schofield 1985, Schebendach *et al*., 1995). The problem with the proposed definition of satisfactory gut function presented above lies in the poor quantification of what constitutes 'tolerance' and 'adequate' nutrition. While it might be tempting to consider adequate nutrition as representing one hundred per cent of calculated nutritional requirements, there is abundant evidence that these assessments often overestimate nutritional needs. In addition, a sizeable proportion of patients, in excess of 60 per cent in some series, fail to achieve these targets intakes (Woodcock *et al*., 2001). There are various reasons for this, including problems with feed delivery systems as well as certain organizational issues which do not necessarily signifying dysfunction of the gut (Mentec *et al*., 2001). This has led authors to arbitrarily adopt lower levels of nutrient delivery to represent 'adequate' nutrition, commonly 80 or 90 percent of calculated requirements (Kan *et al*., 2003; Reid, 2006). One aim of this thesis will be to validate this practice by establishing an acceptable level of calculated nutrients that need to be delivered to represent 'adequate' nutrition.

The other problem with the definition as proposed is the meaning of the word 'tolerance'. In this context the word implies an unspecified period of time (i.e. tolerance of nutrition for a specific number of hours or days). Unfortunately, this concept has not been explored previously, and there is no literature which arbitrary or otherwise designates a period of time for this assessment. Clinically, tolerance is generally assessed hourly on initial commencement of feeding, with a gradual prolongation of the periodicity of assessments in accordance with local feeding protocols. Feeding protocols in different institutions vary in this respect. A pragmatic approach towards establishing a clinically applicable description of adequate and IGF would be to formulate such a definition in terms of tolerance to daily requirements, or multiples thereof, as this would facilitate any necessary calculations and facilitate bedside application.

1.7 POSTPYLORIC FEEDING

Numerous factors may affect the tolerance of an enteral challenge by the gut. One variable that has received considerable attention in recent years is the issue of the site of feed delivery, be this prepyloric (oral or intragastric) or postpyloric (intraduodenal or intrajejunal). It is commonly believed that by delivering nutrients further down the gastrointestinal tract and bypassing the stomach, postpyloric feeding facilitates the tolerance of enteral feeding, and increases the number of patients who achieve this end point (Montecalvo *et al*, 1992; ASPEN, 2002). The rationale is twofold; firstly by bypassing the pylorus problems with gastric atony are avoided and may enhance feed

tolerance. Secondly, delivering feed beyond the pylorus may theoretically minimise the risk of aspiration, with a concomitant improvement in feed build-up and improved adequacy of nutrition (Binnekade *et al*., 2005). If this were to be the case, then defining gut function in terms of enteral tolerance would have to take into account the site of feed delivery and make appropriate corrections for this.

The literature in this respect is poor. Many case control studies have been reported which attest to the safety of postpyloric feeding techniques but there is still relatively little data from prospective and randomised trials. Most randomized trials comparing postpyloric nutrition with prepyloric feeding are intrinsically biased in favour of the former. They fail to take into consideration and then factor in for the major disadvantages of postpyloric feeding, the difficulty and extra time necessary to introduce postpyloric feeding tubes, with the inevitable delay to the instigation of treatment. A bedside technique for postpyloric tube placement could potentially solve these problems (Kreymann *et al*., 2006). This thesis proceeds to describe and validates a novel technique of bedside nasojejunal (NJ) tube placement which will then be used in a randomized controlled clinical trial to compare prepyloric and postpyloric feeding, specifically addressing the question whether tolerance to an enteral challenge is dependent on the site of feed delivery (chapter 6).

1.8 SPLANCHNIC BLOOD FLOW

Physiological changes may be brought about by varying the site of feed administration. However, the effect of feeding on the circulation and more specifically on splanchnic flow is poorly characterised in humans.

The gut is an organ that is exquisitely sensitive to systemic cardiovascular and pulmonary disturbances (Byers *et al*., 1999; Lisbon, 2003). The normal physiological response to systemic hypoperfusion is the shunting of blood away from the splanchnic circulation, towards more vital organs, despite the fact that states of diminished circulatory volume, systemic inflammation and sepsis result in a significant increase in gut and hepatic oxygen consumption (Muller *et al*., 1999). Oxygenation to the villi in man is dependent on a counter current exchange mechanism such that oxygen saturation at the tip of the villi is lower than that of arterial blood. This compounds the normal physiological response to hypoperfusion by rendering the villus very susceptible to ischaemic-reperfusion damage. This is thought to be central to the role of the gut as a motor which drives the onset of delayed sepsis and multi-organ failure, as summarised in the three-hit hypothesis proposed by Deitch and outlined in section 1.3 (Deitch, 2002; Cohen *et al*., 2004).

Diminished splanchnic blood flow as seen in hypovolaemic shock, and bowel ischaemia, is associated with mucosal disruption, increased intestinal permeability (IP) and BT, resulting in or perpetuating septic complications and MOF (Lisbon, 2003). The potential

importance of the therapeutic manipulation of splanchnic flow and its effect on outcome is illustrated in a number of recent human studies which suggest that the use of the splanchnic vasodilator dopexamine is associated with a significant reduction in post-operative morbidity and mortality (Byers *et al*., 1999).

There are a number of ways to increase blood flow to the gut and liver, including correcting hypovolaemia and maintaining an adequate cardiac output. Various inotropic agents, including dopexamine, dobutamine, and dopamine, have vasodilatory properties and may also increase splanchnic blood flow, independent of their effects on cardiac output and blood vessels. The evidence in this respect is often conflicting (Meier-Hellmann *et al*., 1999), probably reflecting the presence of a number of confounding factors such as adequacy of resuscitation, variations in prescribed dosage, and the simultaneous administration of other inotropic agents. Further, different parts of the gastrointestinal tract may show variations in drug response to identical doses of the same inotropic agent (Temmesfeld-Wollbruck *et al*., 1998; Muller *et al*., 1999). This is further compounded by the difficulty to directly assess splanchnic perfusion in humans. The current consensus appears to suggest that dopexamine increases splanchnic blood flow and increases intramucosal pH in sepsis (Smithies *et al*., 1994; Maynard *et al*., 1995; Temmesfeld-Wollbruck *et al.*, 1998; Hiltebrand, Krejci and Sigurdsson, 2004; Asfar *et al*., 2006). Dopexamine may also have other beneficial effects on the gut, not clearly elucidated at this time. These may be mediated by direct anti-inflammatory properties (Tighe *et al*., 1995; Schmidt *et al.*, 1998; Byers *et al*., 1999) or its effect of decreasing amplitude of flow motion in ileal mucosal arterioles (Madorin, Martin and Sibbald,

1999). Most of the quoted evidence is by direct extrapolation from in-vitro or animal trials. In-vivo human studies are needed to clarify the clinical significance of these latter observations. Conversely, dobutamine increases splanchnic blood flow after cardiopulmonary bypass independent of cardiac output (Bastien *et al*., 1999; Ensinger *et al*., 1999). Dobutamine also improve both splanchnic oxygenation and gastric intramucosal pH in septic animals and in septic patients (Neviere *et al.*, 1996; Creteur, De Backer and Vincent, 1999). Dopamine, on the other hand, increases splanchnic blood flow in sepsis (Ruokonen, 1993), which is mediated by numerous vascular dopaminergic receptors found throughout the gastrointestinal tract. The therapeutic applications of increasing splanchnic perfusion remain unclear and require further elucidation.

More recently there has been a resurgence in interest about ways to modulate splanchnic perfusion by nutritional therapy. It is widely accepted that oral alimentation increases gastrointestinal blood flow; however there is a paucity of data regarding the effects of adjuvant modalities of feeding on splanchnic perfusion, in particular, that which occurs with TPN. These poorly defined haemodynamic effects of adjuvant feeding may be important to consider, particularly as there is some suggestion that nutrition may affect ischaemia-reperfusion injury to the gut. For this reason, this thesis describes a study aimed at defining changes in splanchnic blood flow associated with the use of different modalities of nutrient delivery (chapter 7).

1.9 GUT-DIRECTED THERAPIES AND THE MODULATION OF GUT FUNCTION

The possibility that gut dysfunction drives disease processes infers that therapies that attenuate gut failure or preserve gut function may, in theory at least, improve patient outcome by preventing the deleterious cascade of events resulting in delayed sepsis, MOF and death. Since the state of gut function is currently undefined, no therapeutic regimen can set claim to improving gut function or attenuating gut failure, as there exists no yardstick by which improvement can be measured.

Notwithstanding, there are a number of methods by which gut function might, in theory, be modulated (Table 1.3). These include physical methods such as early postoperative mobilisation (Basse *et al*., 2002; Gatt *et al*., 2005; Mythen, 2005; Fearon *et al*., 2005), the use of certain drugs such as prokinetics (Traut *et al*., 2008) or the avoidance of others such as opiates (Kurz and Sessler, 2003). The use of GSN is receiving much interest and will be investigated in chapter 8. GSN are a group of nutrients that include prebiotics (beneficial bacterial strains) and probiotics (fermentable plant fibres), the amino acid glutamine, certain vitamins, antioxidants and trace elements (Duggan, Gannon and Walker, 2002). As a group, these nutrients have a beneficial effect on the gut and its luminal microflora over and above their roles as simple nutrients. In other words, GSN may be defined as those substances that have been demonstrated to have specific effects on gut function, morphology, ecoflora or physiology, over and above any properties as nutrient substrates (Duggan, Gannon and Walker, 2002) and an extensive literature exists

- Physical methods
- Drugs
- Gut specific nutrients
- Synbiotics (pro- & prebiotics)
- Modulation of gut microflora (SGD)
- Immunomodulation
- Other

- Combined approaches (multimodal optimization / ERAS)

Table 1.3: Possible methods to modulate gut function.
(SGD, selective gut decontamination; ERAS, enhanced recovery after surgery)

on their usage.

Indeed there are many other individual or combined approaches that may modulate intestinal function, including multimodal optimization packages (Kehlet and Holte, 2001; Anderson *et al*., 2003; Fearon *et al*., 2005; Gatt *et al*., 2005) as has been shown in section 1.6. Multimodal optimization packages involve many of the strategies mentioned above (Kehlet and Wilmore, 2005; Fearon *et al*., 2005). Their implementation has been reported to attenuate the transitory gut dysfunction that occurs after surgery which has led some authors to speculate whether the benefits of such programmes in fact relates to an enhanced recovery of gut function (Gatt *et al*., 2005).

1.10 HYPOTHESIS

There is ample published literature to suggest that the state of gut function conditions the integrity of the intestinal barrier, influences BT and affects the development of ensuing sepsis and MOF. The adequacy of gastrointestinal function also dictates which routes of nutrition can be used (be this enteral or parenteral), as well as the time feeding can be instigated (be this early or late). All these factors have been associated with patient outcome and therefore support, but do not prove, the contention that the state of gut function may be important to patient prognosis. In addition, the corollary of this argument also may have some validity. Interventions directed at attenuating the period of IF (such as multimodal optimization) appear to have beneficial effects on outcome.

However, the mechanisms which bring about these improvements remain unclear.

The central hypothesis of this thesis is that the state of gut function influences the outcome of patients. As a result, therapies that attenuate gut failure or otherwise enhance the recovery of gut function could possibly improve patient outcomes. This thesis will endeavour to explore this premise by investigating the poorly recognised phenomenon of gut dysfunction and its effect on patient prognosis.

A major impediment in this field of research is that clinicians are poor at assessing gut function clinically. Additionally there is as yet no objective and quantifiable definition for what constitutes normal gut function, and therefore what constituted a state of gut failure. Subsequent chapters of this thesis will attempt to develop such a definition, proceed to validate it against patient outcome, and subsequently using this definition, endeavour to develop a therapy to attenuate gut failure in an attempt to benefit patients.

CHAPTER 2:

AIMS & METHODS

"Great things are not done by impulse,

but by a series of small things brought together."

Vincent van Gogh,
1853 – 1890

2.1 AIMS OF THIS THESIS

There is much circumstantial evidence implicating the gut as a motor of disease, but definitive proof that gut function conditions the outcome of patients is lacking. Progress in this area has been hindered by the lack of a quantifiable definition for IGF, a rationale succinctly summarised by an axiom which states that:

"What cannot be defined cannot be measured;
what cannot be measured cannot be improved,
& what cannot be improved will eventually deteriorate"

(Anonymous)

It is both possible and plausible that the unrecognized effects of IGF are having deleterious consequences to patient prognosis in daily clinical practice. For this reason, and on the background of the literature review and subsequent hypothesis presented in chapter 1, the main aims of this thesis will be:

1. To investigate the effects of multimodal optimization on patients undergoing major surgery and the result of implementation on the restitution of normal gut function (chapter 3).

2. To develop and then validate a quantifiable definition of what constitutes adequate as opposed to IGF (chapters 4 & 5).

3. To establish the importance of the site of feed delivery (prepyloric *versus* postpyloric), if any, on achieving enteral tolerance (chapter 6)

4. To investigate the effects of different modalities of feeding on splanchnic blood flow (chapter 7).

5. To develop a gut-directed therapy intended to maintain or enhance the recovery of normal gut function while attenuating gut failure. The effects of this therapy on outcomes will also be investigated (chapter 8).

2.2 SEQUENCE OF STUDIES

All studies were performed at Scarborough Hospital under the auspices of the Combined Gastroenterology Research Unit, and the Scarborough Hospital Multidisciplinary Nutrition Team. Work towards completion of these trials, including the writing of protocols, submission for ethical and administrative approval, informed consent, patient recruitment, specimen collection, data gathering and compilation, statistical analysis, and final write-up was performed by the author except where specifically mentioned in the relevant sections. Due recognition to the work of others has been given where appropriate. A total of eight clinical studies will be described, with the second study in this series representing a re-analysis of data previously published by other authors.

The first trial (chapter 3) will be a randomized clinical study investigating the merits of

implementing a multimodal optimization package for patients undergoing major colorectal surgery. In common with other published trials results of this study might add to the body of circumstantial evidence supporting the clinical importance of the state of gut function. However, interpretation of results is envisaged to be hindered by the lack of a quantifiable definition of adequate as opposed to IGF.

This need for a quantifiable definition for gut function will be pursued in the second and third studies (chapter 4). These two observational studies will aim to establish a definition of normal gut function (as opposed to gut failure) based on the tolerance by the gut of a quantifiable enteral challenge. Prospective validation of this definition for gut function will then be pursued in a fourth study by investigating the association between the state of gut function and patient mortality (chapter 5).

When defining the state of gut function in terms of enteral tolerance, consideration needs to be given to physiological changes that may be brought about by varying the site of feed administration. This will be investigated by three separate studies. The fifth study (chapter 6) will be an observational study aimed at developing a bedside technique of placing postpyloric tubes. As shall be described, this is considered essential groundwork for the subsequent study (chapter 6). This sixth study will be a randomized clinical trial whose aim will be to investigate the importance of the site of enteral feed administration (prepyloric or postpyloric) on the ability of the gut to achieve enteral tolerance (and therefore on the state of gut function). In the seventh study (chapter 7) presented in this thesis, the effects on splanchnic blood flow caused by varying the site of feed

administration from the enteral route to the parenteral route will be assessed.

Finally, an eight study (chapter 8) will investigate whether the state of gut function can be modulated by GSN, and what effects, if any, a change in the return of gut function will have on patient outcomes. The methodology employed will be that of an externally randomised, double blind, placebo controlled clinical trial in a cohort of critically ill patients.

2.3 PATIENTS, ETHICS AND INFORMED CONSENT

All interventional studies were granted ethical approval by the Locally Organized Research Ethics Committee (LREC) at Scarborough Hospital. Details regarding informed consent are described in the relevant chapters. All patient information leaflets and consent forms were assessed by the same review process prior to commencing recruitment to the trials. LREC trial numbers are provided where relevant.

2.4 MEASUREMENTS

Numerous tests and assays were performed in the 8 clinical trials presented in this work. This section describes research measurements (intestinal permeability, IP) and tests (aspirate pH, CRP and serum albumin) common to more than one trial. Further details

about these and other measurements are also provided in the methods sections of the relevant chapters.

2.4.1 Intestinal permeability

The permeability of the intestinal wall to macromolecules has been investigated using inert sugar probes. The passage of these probes from the intestinal lumen, across the membrane, into the circulation and subsequently into a patient's urine has been assumed to assess the structural integrity of the gut membrane, and therefore to somehow correlate with intestinal barrier function. However to this date the clinical relevance of this test remains unclear. As such, its availability is limited to a few institutions with an interest in investigating the physiology of the alimentary tract, and as such remains a research tool. Numerous authors have documented increased IP associated with critical illness (Deitch, 1990; Ammouri *et al*., 1999; Spindler-Vesel *et al*., 2007) and other diseased states. It is this observation that has further promoted the general assumption that changes to macromolecule permeability reflects abnormalities of barrier function, which in turn may predispose to BT, sepsis and MOF. This is a theoretical assumption, which has not yet been borne out in clinical trials (O'Boyle *et al.*, 1998[b]; McNaught *et al*., 2002; Jain *et al.*, 2004).

The intact intestinal mucosal membrane acts as a physical barrier and prevents the passive movement of non-charged water soluble compounds with a molecular size of

>0.4 nm (Menzies, 1984; Travis, 1992). Whether this property extends to bacteria and other micro-organisms is questionable. Permeability assays rely on the differential absorption and subsequent urinary excretion of orally administered probes (often sugars) of distinct molecular weights. The larger molecules (e.g. lactulose) are presumed to pass between enterocytes and therefore represent a measure of leakiness of the intracellular tight junctions. Conversely, smaller molecules (such as rhamnose) are supposed to take the transcellular route (i.e. through the enterocyte) (Menzies, 1984; Travis, 1992).

There are a few concerns with standard permeability assays however. At best, customary dual sugar probe permeability assays are estimates of small bowel properties only, and provide no information about colonic permeability. This is because the sugar probes are digested by enteric bacteria (Meddings and Gibbons, 1998) such that little of the probes can be found beyond the ileo-caecal valve. A novel triple sugar test described by Anderson *et al*. uses lactulose and rhamnose probes together with the indigestible sugar sucralose. It has been validated to address the problem of probe digestion in the colon and is the IP test that has been used throughout this thesis (Anderson *et al*., 2004; Anderson *et al*., 2005). This test permits evaluation of small intestinal permeability (assessed from the lactose:rhamnose (L:R) ratios), total intestinal permeability (assessed from sucralose concentrations) and colonic permeability (assessed by subtracting small intestinal permeability from total intestinal permeability).

Briefly, the method involves subjects being fasted from midnight and then administered an accurately measured triple sugar probe solution between 08:30 and 09:30 the

following morning. Patients are asked to drink 30ml of water containing 5g sucralose (analytical grade micronized powder, McNeil Nutritionals, NJ, USA), immediately followed by 120ml of water containing 5g lactulose (7.5ml Duphalac® syrup, Solvay Pharmaceuticals, Marietta, Georgia, USA) and 1g rhamnose (analytical grade powder, BDH Laboratory Supplies, Poole, UK). After ingestion, the patients are allowed to drink water for the first 5 hours and to eat and drink freely following this, should their clinical condition permit. Once the sugar probes are administered, a 24h urine collection is commenced. Urine passed during the first 5 hours is collected separately from that passed during the last 19 hours. Both are collected into apposite containers prepared with 1ml merthiolate as a preservative. On completion of the 24 hour urinary collection, two 10ml aliquots of the 5h urine are sampled and stored at –40 ^{o}C in appropriately labelled plain universal containers. The remaining 5h urine sample is then mixed with the 19h urine sample and a further two 10ml aliquots of this 24h specimen are similarly stored at –40 ^{o}C in appropriately labelled plain universal containers.

For the purposes of this thesis, all the urine samples collected for IP assays were batched and sent to a reference laboratory in Truro, Cornwall, United Kingdom to be processed using the same technique described and validated by Anderson *et al*. (2004 and 2005). Urinary lactulose and L-rhamnose concentrations were assessed using HPLC with pulsed amperometric detection (coefficient of variance (CV) for these tests were respectively 5.84% and 2.91%) while sucralose concentrations were assayed using HPLC with a refractive-index detector (Gilson 133, Gilson Inc., Middleton, USA). Sucralose concentration estimations had a between-batch CV of 6.07% (Anderson *et al*. 2004).

2.4.2 Gastric and postpyloric aspirate pH

Two methods were employed to test gastric and postpyloric aspirates for pH. The first made use of reagent strips widely available on general medical and surgical wards (Multistix® 10 SG, Bayer Diagnostics Mfg., Ltd. Bridgend, UK). These permitted visual pH estimates of between 5 and 8.5. These reagent strips were used as a pragmatic method of pH assessment because of their wide availability on general medical and surgical wards. However, because these reagent strips were only licensed to assess urinary pH, a second method of assessing enteral aspirate pH was used for purposes of confirmation. This employed the use of an electronic handheld pH meter (Hanna pH tester, Progen Scientific Ltd, Mexborough, UK) which was regularly calibrated as recommended by the manufacturer. This gave digital pH readings between the pH of 0 and 14 to the closest two decimal points. Given a perfect positive correlation ($r = 1.000$) between the two methods of pH assessment in a cohort of 96 patients (results not shown), only results from reagent sticks will be presented. Further details relating to the sampling of gastric and postpyloric aspirates are provided in the appropriate chapters.

2.4.3 Serum C-reactive protein

CRP is a member of the pentraxin family of proteins and is characterized by a cyclic pentameric structure and radial symmetry. It is produced by the liver as one of the 'positive' acute-phase proteins where blood levels of CRP rise by orders of magnitude as

part of a general, unspecific response to infectious as well as to non-infectious inflammatory processes. Amongst its many physiological roles, CRP acts as a ligand for specific receptors on phagocytic leukocytes, it mediates activation reactions on monocytes and macrophages, and also activates complement (Gruys *et al*., 2005). Increased production of CRP and similar 'positive' acute phase proteins is associated with a concomitant decrease in synthesis of other blood proteins such as transthyretin (formerly called prealbumin), retinol binding protein, cortisol binding globulin, transferrin and albumin, which together represent the 'negative' acute phase proteins.

Increases in hepatic CRP production results from a hepatic mRNA upregulation in response to stimuli such as infection, ischemia, trauma, burns, and other inflammatory conditions, and can be detected in patients' serum. Raised serum CRP levels are both qualitative as well as quantitative in providing an indication as to the presence and extent of an inflammatory process. For conventional CRP assays, test values are typically considered to be clinically significant at levels above 10 mg/L. In apparently healthy subjects, serum CRP levels are below 5 mg/L, while in various conditions this threshold is often exceeded within four to eight hours after an acute inflammatory event, with CRP values reaching approximately 20 to 500 mg/L (Kushner and Rzewnicki, 1994).

For purposes of this thesis, appropriate blood samples were collected by the author. Specifics relating to the periodicity of collection are provided in the appropriate methods sections of subsequent chapters. Serum CRP assays were then performed by laboratory staff in the Biochemistry Department at Scarborough Hospital using a turbidimetric

method (Synchron CX Systems, Beckman Coulter Inc., Fullerton, CA, USA). The process of CRP level estimation was fully automated and involved mixing the serum with a reagent containing specific anti-CRP antibodies, forming insoluble antigen-antibody complexes. This caused a change to the mixture which could be detected by a change in the absorbance measured at a wavelength of 340 nm. This change was proportional to the CRP concentration in the specimen, the concentration being calculated based upon a non-linear calibration curve. The intra-assay coefficient of variatiance (CV) for this test was 4.7 per cent, while the inter-assay CV was 6.9 per cent.

2.4.4 Serum albumin

Albumin represents one of the 'negative' acute phase proteins, with a reduction in serum levels occurring as a consequence of the acute phase response. Serum levels were considered to be within the reference range between the concentrations of 38 and 47 g/L.

For purposes of this thesis, appropriate blood samples were collected by the author. Specifics relating to the periodicity of collection are provided in the appropriate methods sections of subsequent chapters. Serum albumin assays were then performed by the laboratory staff in the Biochemistry Department at Scarborough Hospital using routine autoanalysis (Cobas Integra 800, Roche Diagnostics Ltd., Lewes, UK). As part of this automated process, the serum sample was mixed with the anionic dye bromcresol green at a pH of 4.3. This binds to albumin to form a blue/green coloured complex imparting a

similar colour to the sample which can be assayed using light absorbance methods. The absorbance of the mixture was measured at a wavelength of 629 nm, with the intensity of the blue/green colour being directly proportional to the serum albumin concentration, which was calculated automatically based on a non-linear calibration curve. The intra-assay CV was 1.2 per cent, while the inter-assay CV was 1.5 per cent.

2.4.5 Other serum and blood assays

Numerous other assays were performed in this series of studies. These included full blood count and white blood cell differential estimations, electrolytes and liver function tests, together with lipid and coagulation profiles as well as zinc, phosphate, magnesium and calcium levels. Other investigations were also requested on an individual basis as deemed necessary by the attending physicians. All these investigations were performed in the Biochemistry Department at Scarborough Hospital according to standardized protocols. Procedures for performing these assays were validated by means of regular calibration and rigorous quality control as per hospital and laboratory policies. It is beyond the scope of this work to review the methodology employed in all these assays, however, where relevant, further details are mentioned in the respective chapters.

2.5 STATISTICS

Results were tabulated on an Excel® spreadsheet (Excel for Windows®, Microsoft Corporation, Redmond, Washington, USA) and then analysed using SPSS® for Windows® version 11.5 (SPSS®, Chicago, Illinois, USA).

The specific statistical methods used in each of the studies in this thesis have been described in more detail in the respective chapters. In broad terms, continuous variables with a normal distribution were expressed as means and standard deviations (SD), while skewed data were presented as medians and interquartile ranges (IQR). Relationships between groups were assessed using χ^2 test for binary outcomes or Fisher's exact test for small cohort as appropriate. Continuous variables were compared with the Student's *t*-test for parametric data or the Mann-Whitney *U*-Test as a non-parametric alternative. Paired non-parametric quantitative data were compared using the Wilcoxon signed rank test, and changes over multiple time points within groups were analysed using Friedman's test.

Where appropriate, other characteristics for binary outcomes were also calculated. For a given binary outcome, where the corresponding 2x2 table is represented by:

	Outcome Occurred	Outcome did not Occur	Totals
Risk Factor Present or Test Positive	a	b	r1
Risk Factor Absent or Test Negative	c	d	r2
Totals	c1	c2	t

Sensitivity (a/c1), specificity (d/c2), positive predictive valve (a/r1), negative predictive value (d/r2), number needed to diagnose (1/{Sensitivity – [1–Specificity]}), and number needed to treat (1 / [a/r1] - [c/r2]), were established as indicated in parenthesis.

Where multiple factors were assessed for independent association, data points were individually assessed for association using univariate statistical methods as previously described. Factors which were significant on univariate analysis were subsequently evaluated for independent association using multivariate logistic regression. Survival analysis was performed using the Kaplan-Meier method.

Statistical significance was considered at the 5 percent level and where relevant, data was analysed on an 'intention-to-treat' basis. Sample size calculations were performed where necessary. These were formulated to show differences with at least 80% power, and calculations were based on published data when this was available. The details of individual power calculations and degrees of power are highlighted in the respective chapters.

2.6 ABBREVIATIONS AND SCORING SYSTEMS

Numerous abbreviations are used throughout this manuscript. The first time an abbreviation appears, it is preceded by the words for which it stands. A complete list of abbreviations is listed on pages 21 and 22. Numerous scoring systems have also been used throughout this work and are summarised in appendix 3.

2.7 UNITS OF MEASUREMENT

The modern metric system of measurements for the quantification of data known as the International System (SI) of Units is used throughout this thesis (Taylor (ed.), 1995; Taylor (ed.), 2001).

CHAPTER 3:

MULTIMODAL OPTIMIZATION OF SURGICAL CARE AND ITS EFFECTS ON THE RETURN OF GUT FUNCTION

'It is not a question of how well each process works, the question is how well they all work together.'

Lloyd Dobyns and Clare Crawford-Mason,
Thinking About Quality,
Contemporaries

Work from this chapter has been published in an article entitled 'A randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection' (Gatt M. et al., 2005).

3.1 INTRODUCTION: MULTIMODAL OPTIMIZATION

Much has been published about multimodal optimization in the management of surgical patients (Kehlet and Wilmore, 2002; Anderson *et al*., 2003; Fearon *et al*., 2005; Gatt *et al*. 2005; Kehlet and Wilmore, 2005; Wind *et al*., 2006). Common to all enhanced recovery programmes is an attempt to attenuate the surgical stress response, accelerate recovery, decrease complications, shorten hospitalisation and reduce health costs, all without compromising patient safety. The mechanisms by which such improvements are brought about are not well characterized, but it has been suggested that they may partly be a consequence of an enhanced recovery of gut function (Gatt and MacFie, 2005; Wakeling *et al.*, 2005). The aim of this trial was to assess the effects of a multimodal optimization package on patients undergoing major colorectal surgery in the setting of a randomized clinical study. The effects of multimodal optimization on the recovery of postoperative gut function were specifically recorded.

3.2 PATIENTS AND METHODS

Based on published data (Anderson *et al*, 2003), a sample size calculation showed that a minimum of 19 patients would be required in each group in order to demonstrate a reduction in length of stay of 2 days at the 5% level of significance with a power of 90%. To this end, and following approval by LREC (Ref. No. PB/rh/02/329), 52 consecutive patients requiring elective colorectal surgery were identified. Eight patients were excluded as they did not satisfy the inclusion and exclusion criteria: 3 did not consent to

be included in the trial, 2 were on anticoagulant medications, 2 were not living independently at home and one patient was predicted to require prolonged hospitalization for additional staged surgical interventions. Subject to informed consent the remaining 44 patients were recruited. Other inclusion and exclusion criteria are summarised in Table 3.1. 5 patients were subsequently excluded from data analysis: 2 required emergency surgery, 2 patients were envisaged to require prolonged hospitalisation for factors unrelated to surgery (both because of a sudden change in social circumstances), and a colonic resection was not performed on one patient due to advanced disease not detected on preoperative assessment. Of the remaining 39 patients, 19 were randomized to receive multimodal optimization (optimized group), the other 20 being treated conventionally (control group). Randomization was by means of opening of sealed envelopes previously labelled by an individual outside the research team according to a list of randomly generated numbers. Patients were followed from preoperative recruitment to 30 days after surgery, and operative severity was assessed using POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity) scores. Details of the surgical procedures performed in each group and POSSUM operative severity scores are summarised in Table 3.2, while the overall study design is summarised in the flow diagram represented in Figure 3.1.

Inclusion criteria	Exclusion criteria
• All patients requiring elective colorectal surgery • Living independently at home	• Failure to obtain consent • Age <18 years • Pregnancy • Intolerance to probiotics and/or prebiotics • Contraindication to one or more optimization strategy • Contraindications to early postoperative discharge • Prescribed medications that may independently prolong stay (e.g. anticoagulants) • Advanced malignancy on preoperative assessment • Palliative surgery • Emergency surgery • Failure to perform colonic / rectal resection

Table 3.1: Inclusion and exclusion criteria

Operation	Control group	Optimized group	P-value
Right hemicolectomy	**5**	**5**	**-**
Left hemicolectomy	**2**	**0**	**-**
Sigmoid colectomy	**0**	**2**	**-**
Hartmann's procedure	**1**	**0**	**-**
Anterior resection	**5**	**10**	**-**
Subtotal colectomy	**3**	**0**	**-**
Panproctocolectomy	**2**	**1**	**-**
Panproctocolectomy and pouch	**0**	**1**	**-**
Abdominoperineal resection	**2**	**0**	**-**
POSSUM operative severity score*	**12 (11 - 16)**	**13 (11 - 15)**	**0.989**

Table 3.2: Operative record and POSSUM operative severity scores.

* Values are medians (IQR)

(POSSUM, physiological and operative severity score for the enumeration of mortality and morbidity)

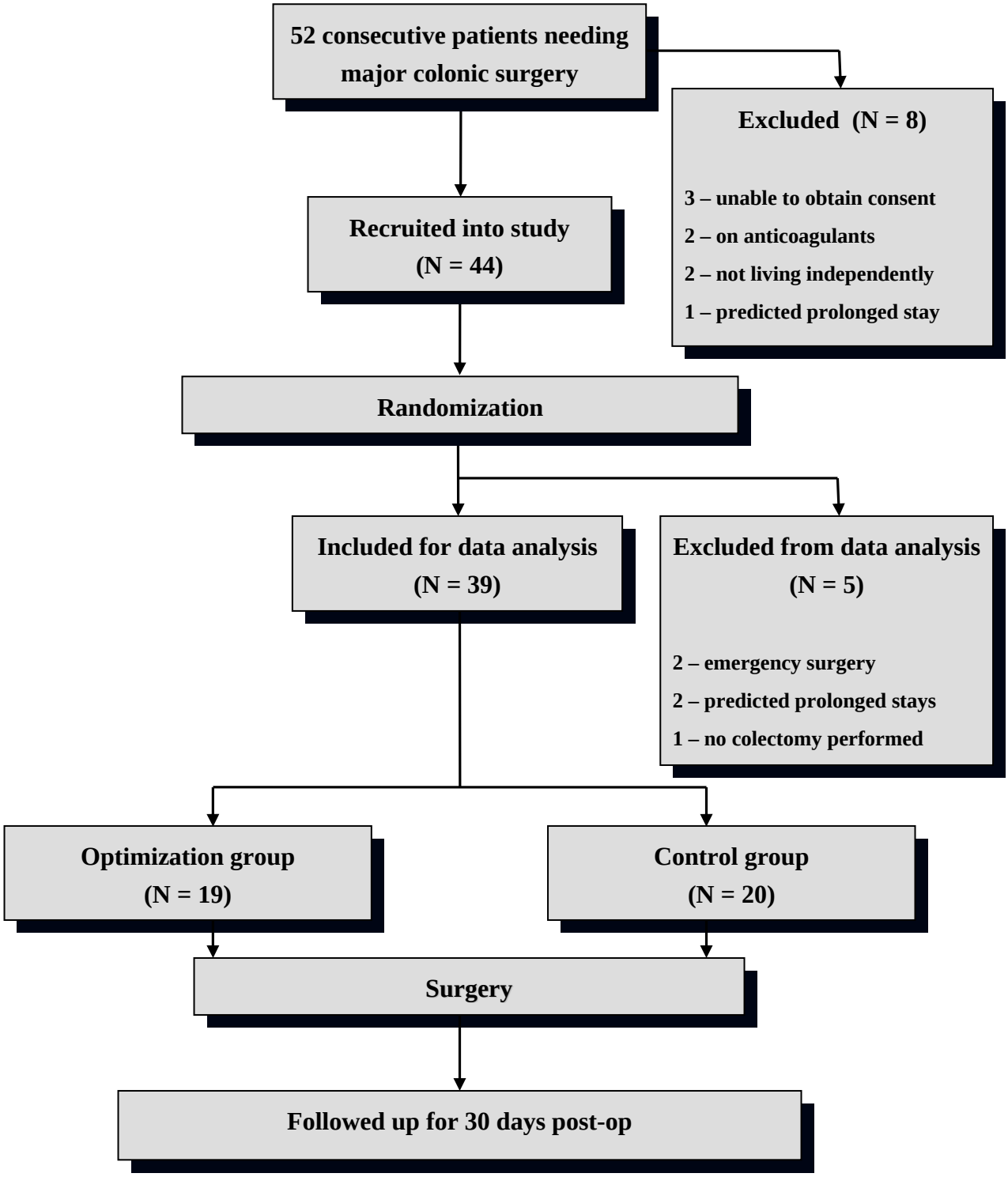


Figure 3.1: Flow diagram of overall study design

3.2.1 The optimization package

A 10-point optimization package was implemented in patients randomized to this group. This package was put together in such a way as to encourage the earlier return of gut function after surgery and involved preoperative, peroperative, and postoperative strategies (Table 3.3).

On entry into the trial, patients received both verbal and written information about the operation and the postoperative rehabilitation programme. A probiotic Trevis® (Chr. Hansen, Horseholm, Denmark) in a dose of one capsule three times daily, along with the prebiotic oligofructose (Orafti USA, Malvern, USA) in a dose of 15g daily were prescribed for 7-14 days before the operation. Each capsule of Trevis® contained $4x10^9$ colony forming units of *Lactobacillus acidophilus La5, Lactobacillus bulgaricus, Bifidobacterium lactis Bd-12* and *Streptococcus thermophilus*. Patients were admitted the day before surgery and were allowed to eat and drink freely until midnight. A drink containing 100g carbohydrate (Maxijul® 500 Super Soluble, SHS International Ltd, Liverpool, UK) in 400ml of water was administered at 22.00 hours and a further 50g of carbohydrate in 400ml of water was given 3-4 hours before the operation. Patients did not receive bowel preparation.

Peroperatively, patients were maintained on high (80%) inspired oxygen concentrations. Transverse abdominal incisions were performed whenever possible. No drains were left at the end of the procedure and any nasogastric (NG) tubes placed peroperatively were

	Treatment parameter	Reasons for inclusion
Preoperative	Verbal and written pre-operative information	↓anxiety, pain & hospital stay, ↑compliance with aggressive rehabilitation, ↓ileus.
	Pre-assessment by surgical registrar or anaesthetist	To confirm suitability for optimization.
	Synbiotics (i.e. probiotics & prebiotics)	Beneficially modulate resident gut microflora, ↑anastomotic healing, ↓postoperative infections.
	Avoidance of mechanical bowel preparation	Similar anastomotic leakage and septic complications, improved outcomes, ↓patient stress, avoidance of electrolyte imbalances & dehydration.
	Oral carbohydrate loading & 3 hour preoperative fast	Safe, ↓postoperative insulin resistance, improved outcomes after surgery.
Peroperative	High inspired O_2 concentrations (80%)	↑intestinal intramural oxygenation, ↓risk of wound infections, ↓postoperative nausea & vomiting
	Transverse incision	↓pain, ↓chest infections, encourage earlier feeding and return of gut function, ↑ambulation, ↓hospital stay.
	No drains or nasogastric tubes	No evidence of benefit in their use, ↓mobilisation, ↑patient distress.
Postoperative	Early fluid & diet reintroduction	Safe & probably advantageous, ↓septic complications.
	Aggressive structured mobilisation plan	↓ileus, complications of abdominal surgery, & hospital stay

Table 3.3: The optimization package and reasons for inclusion of individual strategies (see text for appropriate references).

removed on completion of the surgery. Postoperatively, patients were allowed fluids immediately, and diet was introduced as tolerated following this. A structured mobilisation plan which involved the active intervention from physiotherapists was adopted. This involved sitting patients out of bed on the day of surgery, and walking the length of the ward on the first postoperative day. Further mobilisation was encouraged depending on patient tolerance.

Analgesia was standardised throughout the perioperative period. Patients in both groups received epidural analgesia through a catheter placed between T7 and L1 levels immediately before surgery. Following an initial bolus of 15–20ml of 0.25% bupivacaine, a combination infusion of 0.15% bupivacaine and 2μg/ml fentanyl was used to cover the intraoperative period and then continued for 24 to 36 hours postoperatively. Induction was achieved using a combination of fentanyl, propofol and atracurium; patients were then maintained on sevoflorane (1.0 – 1.2 minimum alveolar concentration) and medical air, supplemented with oxygen to achieve the appropriate oxygen concentration. Reversal was achieved using 2.5mg neostigmine and 0.5mg glycopyrronium. Postoperatively patients were prescribed oral paracetamol (1g, four times a day) and ibuprofen (400mg, as required up to three times a day), while opiate analgesics were avoided except for purposes of rescue analgesia.

3.2.2 Control protocol

Patients randomized to the control arm received none of the optimization measures listed in Table 3.3. Patients were provided with an information sheet briefly describing the study, but this did not include data about the optimization strategies utilized. Patients randomized to the control arm were preassessed by junior doctors under the supervision of an anaesthetist as is customary for all patients requiring surgery in Scarborough hospital. Synbiotics were not prescribed. Following admission a day before surgery, patients received bowel preparation and were fasted from midnight.

At surgery, vertical (midline or paramedian) incisions were used, and NG tubes and abdominal drains were placed according to the surgeon's preference. Postoperatively, patients had oral fluids and diet reintroduced in a traditional stepwise manner as deemed appropriate by the attending surgical staff. The time from surgery to the re-introduction of fluids and diet were recorded for purposes of comparison. All received postoperative chest physiotherapy and were mobilized by nursing staff.

3.2.3 Blinding

In common with other fast-track trials, it was not possible to blind this study. In an attempt to decrease bias, objective discharge policies were standardised. Patients were only considered for discharge when they were able to tolerate three light meals a day,

mobilise safely, and were free of all but oral medications.

3.2.4 End points

Patients were assessed twice a day by a single researcher for the duration of their hospital stay. The author also followed patients up after discharge in an attempt to minimise observer bias. Data was collected before operation, on the day of surgery, daily thereafter until discharge, and on days 7 and 30 postoperatively. Multiple outcome measures were recorded (Table 3.4), and the primary end point was length of hospitalisation.

Physiological function: Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were recorded using a portable spirometer (Vitalograph® Limited, Buckingham, UK). Mid-arm circumference (MAC) and hand grip strength were recorded on the non-dominant side. Hand grip strength was measured in kilograms using a Jamar® dynamometer (NexGen Ergonomics, Montreal, Quebec, Canada). The duration of urinary catheterisation was documented. Strict charting of all input and output was maintained to calculate overall fluid balance. Postoperative mobilisation was recorded daily, assisted by the use of a patient diary of daily activities. The time spent by the patient out of bed on each postoperative day, the time to mobilise to the toilet with help and unaided, and the time to walk the length of the ward with help and independently were all recorded for comparison.

Demographics:	Age
	Sex
	Indication for operation
	Operation performed
	Stoma formation
Physiological Function:	Spirometry (FEV_1, FVC)
	Grip strength (kilograms)
	POSSUM & POSSUM operative severity
	ASA scores
	Duration of catheterisation (hours)
	Time to mobilisation (hours)
	Fluid balance
Psychological Function:	Cognitive function scoring
	Fatigue scoring
	Pain scoring
	Analgesic requirements
Gut function:	Tolerance to fluids & diet (hours)
	Duration of intravenous fluids (hours)
Clinical Outcome:	Length of stay (days)
	Complications & mortality
	Need for readmission
	Overall stay (first 30 days)
	Number of GP visits

Table 3.4: Outcome measures recorded.
(GP, general practitioner)

Psychological end points: 10 cm visual analogue scales without intersections were used to record fatigue and pain scores. Pain assessments were performed at rest, on coughing and on movement. Cognitive function was determined by means of a validated hospital anxiety and depression (HAD) questionnaire (Zigmond and Snaith, 1983). A log was kept of all analgesic requirements after surgery.

Return of gut function: There exists no validated and quantifiable definition of normal gut function in the literature, but for purposes of this trial the return of normal gut function was defined as a patient's ability to tolerate three light hospital meals a day (estimated to represent approximately 80% of a patient's calculated nutritional requirements). Time to achieve this was recorded in hours from the time of surgery. The duration of intravenous infusions postoperatively was recorded as a surrogate indicator of fluid tolerance by the gut.

Clinical outcome: The length of hospital stay and the occurrence of septic and non-septic complications of surgery were recorded, along with data relating to morbidity and mortality. Following discharge, the need for patient readmission and the total number of general practitioner (GP) visits were documented at one month. Total hospital stay (comprising of the length of stay after the index procedure together with the length of stay of any subsequent readmissions during the one month follow-up period) was also recorded.

3.2.5 Statistical analysis

Results were analysed using SPSS® for Windows® version 11.5 (SPSS®, Chicago, Illinois, USA). Results were expressed as medians (IQR). Relationships between groups were assessed using χ^2 test for binary outcomes, while continuous variables were compared with the Mann-Whitney *U*-Test. Changes over time within groups were analysed with Friedman's test. Statistical significance was considered at the 5 percent level.

3.3 RESULTS

Demographics: The two groups were comparable with respect to age, sex, body mass index (BMI), American Society of Anaesthesiologists (ASA) grade, and POSSUM scores (Table 3.5). There were also no differences in the prevalence of malignancy and stoma formation.

Physiological function: Optimized patients spent more time out of bed on the first postoperative day (105 (IQR; 34 – 225) minutes vs. 8 (IQR; 0 – 38) minutes; p=0.047). Furthermore, optimized patients were catheterised for a shorter period of time then patients treated conventionally (respectively 48 (IQR; 38 – 82) hours *vs.* 88 (IQR; 54 – 155) hours; p=0.022). However, the time taken for independent mobilisation to the toilet were similar for both groups (p=0.791). There were no differences with respect to overall

	Control group	Optimized group	p-value
Number of patients	20	19	
Age (years)**	67 (60 – 73)	67 (59 – 76)	0.643
Sex ratio (M:F)	14 : 6	9 : 10	0.151
BMI**	27 (24 – 30)	24 (21 – 29)	0.120
ASA score**	2 (2 – 3)	2 (2 – 2)	0.532
POSSUM score**	32 (29 – 35)	28 (27 – 34)	0.253
Malignant disease	12	15	0.200
Stoma formation	14	13	0.915

Table 3.5: Summary of patient details, ASA and POSSUM scores.

** Values are median (IQR).

ASA, American society of anaesthesiologists;

POSSUM, physiological and operative severity score for the enumeration of mortality and morbidity.

fluid balance on the day of surgery (p=0.500), on the first postoperative day (p=0.888), or on the second postoperative day (p=0.068).

There was a significant difference in grip strength between the two groups preoperatively (p=0.022), and at 1 month after surgery (p=0.015). This difference was not detected in the immediate postoperative period. Grip strength after surgery was maintained throughout in the optimized group (p=0.241, Friedman's test) but was significantly reduced in the postoperative period in patients treated conventionally (p=0.049, Friedman's test). Changes in grip strength are summarised in Figure 3.2.

There was a significant decline in FEV_1 (p=0.007 for optimized patients, p<0.001 for controls; Friedman's test) and FVC (p=0.003 for optimized patients, p<0.001 for controls; Friedman's test) in both groups immediately after surgery. No differences were found between the groups at any time point.

Psychological function: There were no recordable differences between the two groups with regards to serial fatigue and pain scores. Likewise, there was no recordable difference in analgesic requirements, or serial HAD scores.

Gut function: Changes relating to return of gut function are summarised in Figure 3.3 and Figure 3.4. Optimized patients required intravenous fluids for a shorter period of time than controls (respectively 34 (IQR; 24 – 51) hours *vs.* 68 (IQR; 46 – 72) hours; p=0.007). Moreover, patients who received the multimodal optimization package

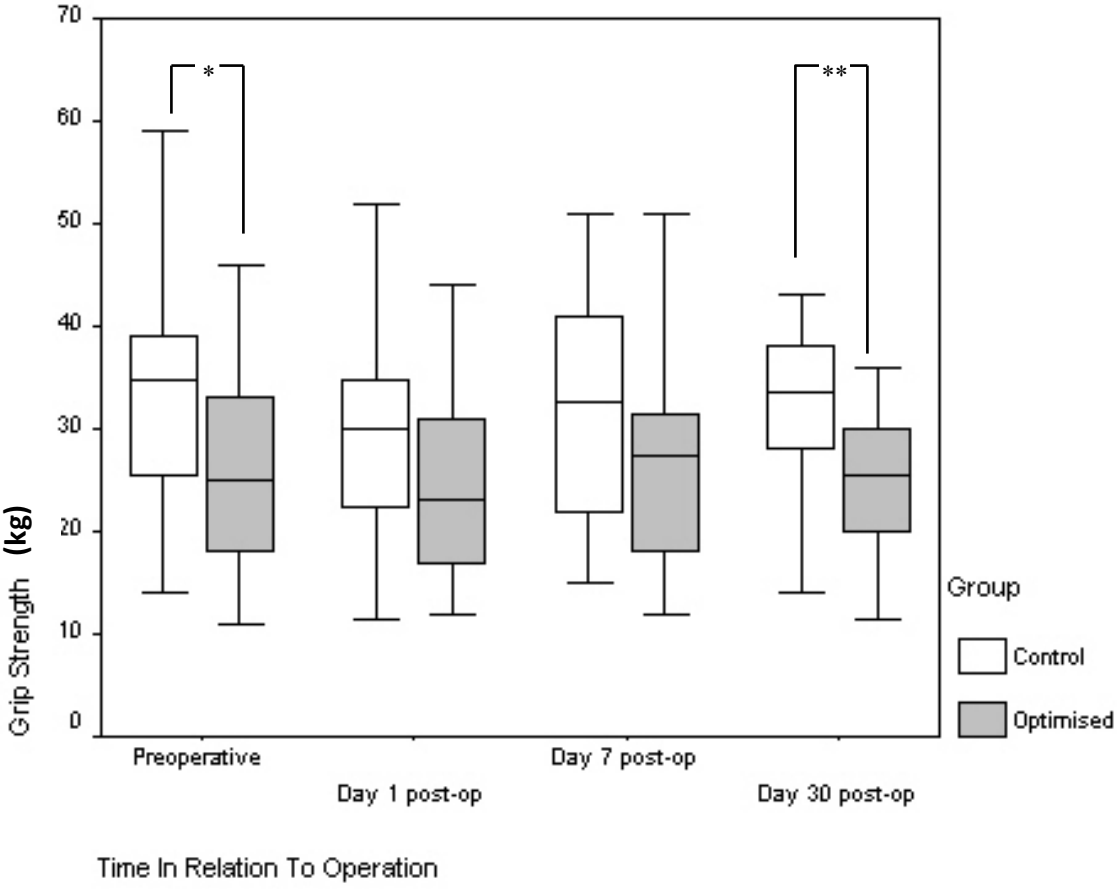


Figure 3.2: Serial grip strength measurements.
(* p=0.022; ** p=0.015)

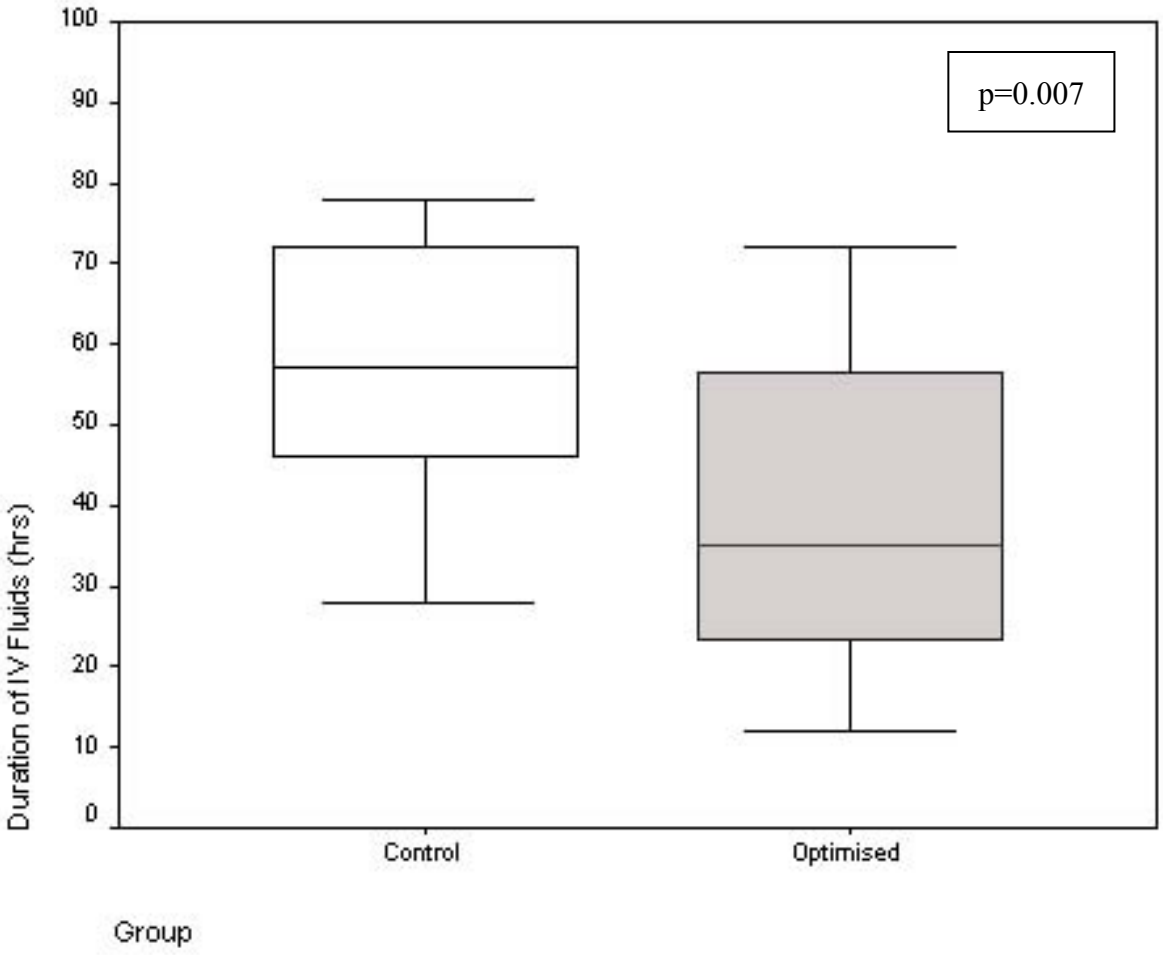


Figure 3.3: Fluid tolerance as assessed by the duration of intravenous fluids from the time of surgery.

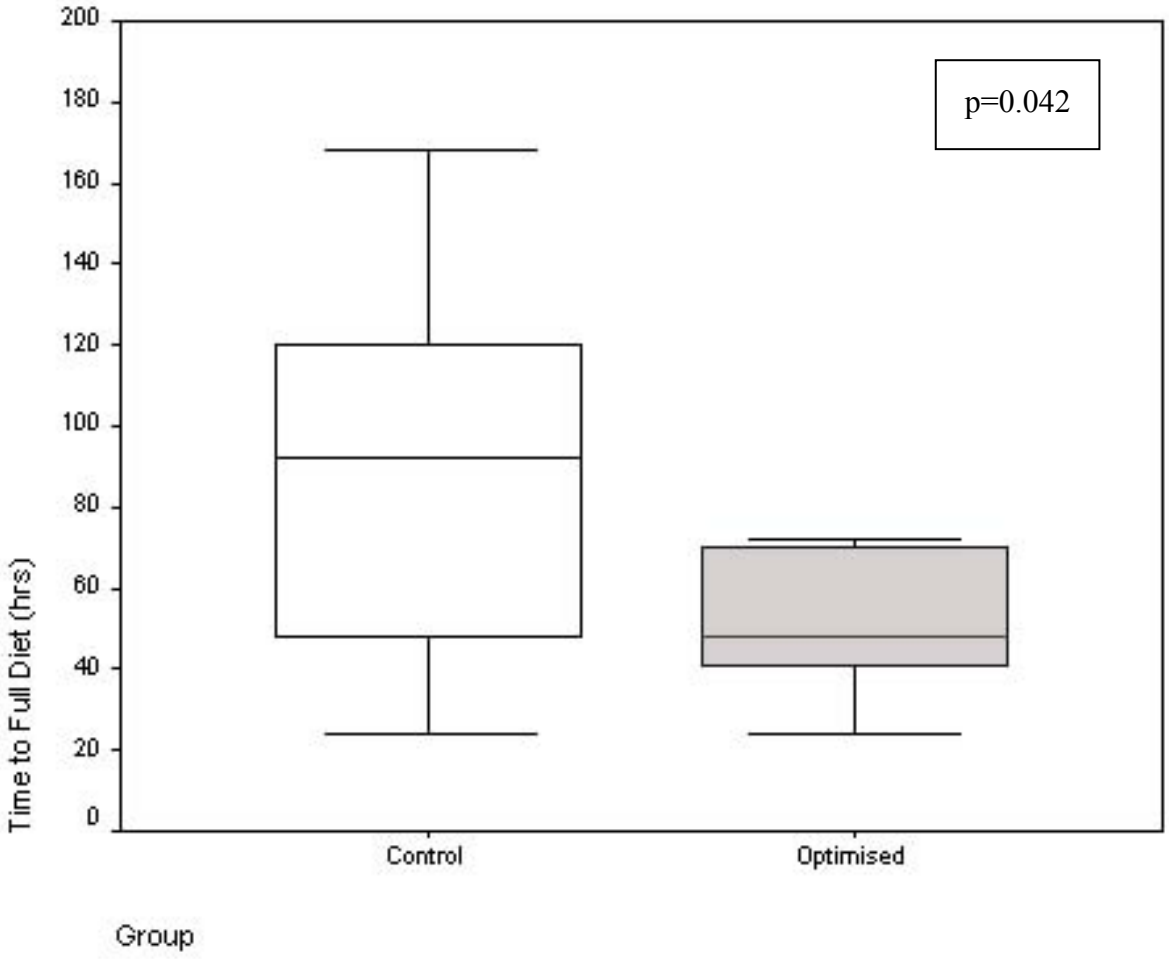


Figure 3.4: Return of gut function as represented by the time to full diet from the time of surgery.

tolerated an oral diet significantly earlier than patients treated conventionally (respectively 48 (IQR; 40 - 71) hours *vs.* 92 (IQR; 48 – 120) hours; p=0.042).

Length of stay: The results for length of hospital stay are illustrated in Figure 3.5. Patients in the optimization group stayed in hospital for a median (IQR) of 5 (4 – 9) days while controls were hospitalised for 7.5 (6 – 10) days (p=0.027). By day 5 from surgery, over 50% of optimized patients compared to only 10% of controls had been discharged.

Morbidity and mortality: 24 patients developed complications (Table 3.6), 9 in optimized patients and 15 in controls (p=0.076). 5 patients needed readmission within 30 days of surgery (respectively 1 vs. 4; p=0.169), and there were observed difference in overall hospital stays between the two groups (respectively 5 (4 – 9.5) days vs. 8.5 (7 – 13) days; p=0.027). The median (IQR) number of assessments by the GP required in the first month after operation (respectively 1 (0 – 1) vs. 0 (0 – 1); p=0.373) were similar in both groups. There was one death in this series and this occurred following a perioperative myocardial infarct in a patient randomized to the optimization arm. This resulted in an overall mortality of 2.6%.

3.4 DISCUSSION

Numerous randomized controlled trials have shown the benefits of multimodal optimization for patients undergoing elective colorectal surgery. Once again the results

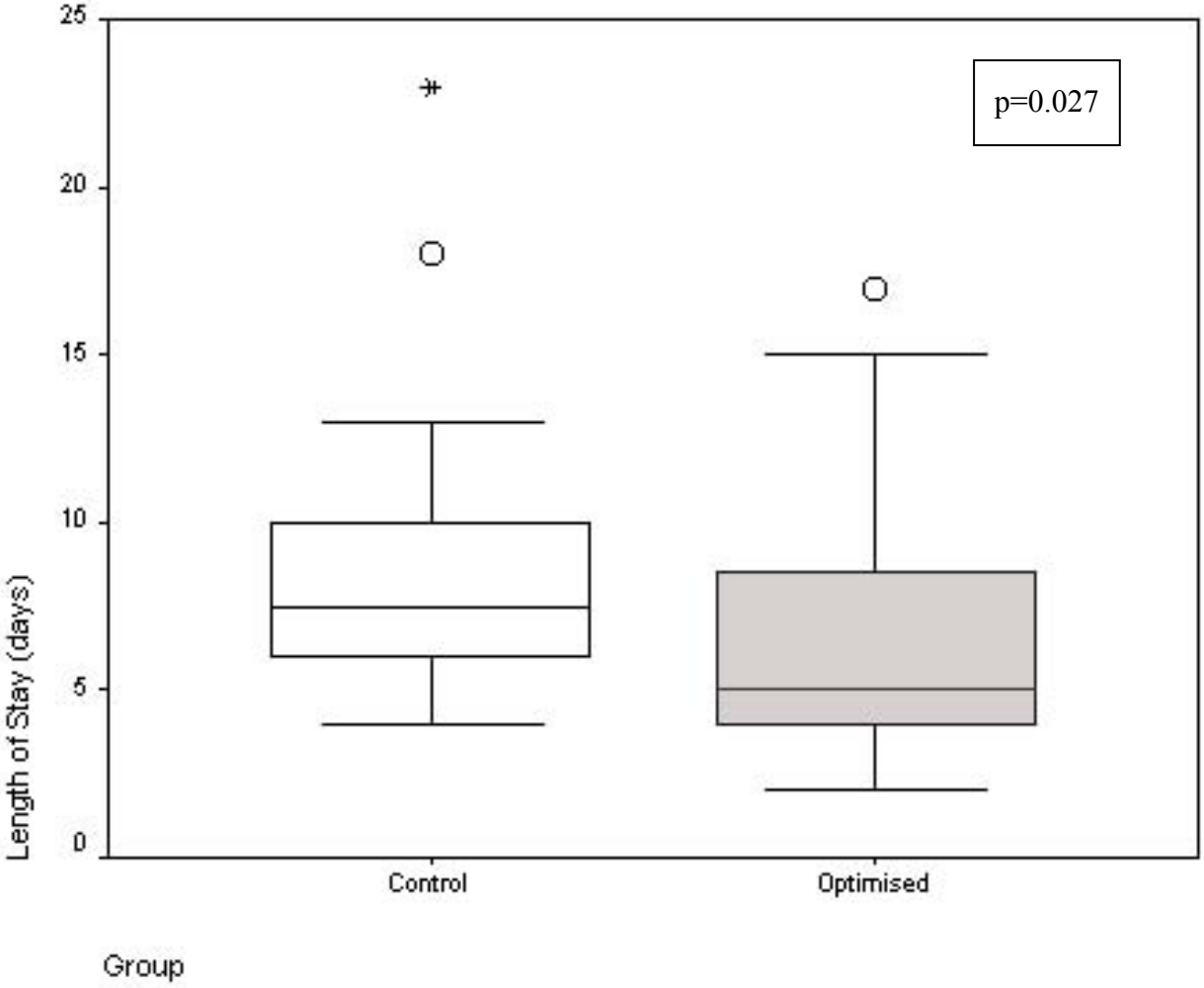


Figure 3.5: Length of hospital stay (shapes represent outliers)

Complications	Control group (n = 20)	Optimized group (n = 19)	p-value
Septic			
Urinary tract infection	2	0	
Wound infection / breakdown	4	0	
Diarrhoea & vomiting	2	1	
Ileus	3	3	
Chest infection	0	1	
Non-septic			
DVT	0	2	
Other	4	1	
Death	0	1	
Total	15	9	0.076

Table 3.6: Complications of surgery

of this study corroborate previously noted benefits of fast-track programmes. Optimized patients required a shorter period of urinary catheterisation, were able to mobilise more quickly, and had an earlier return of gut function. Over 75 percent of fast-track patients had their intravenous infusions discontinued by the end of the second postoperative day, and were on a full diet by day three postoperatively. Optimization enhanced the return of normal gut function and decreased the period of hospitalisation without any measurable increases in morbidity or mortality.

A criticism of the study design is the lack of blinding, a criticism which applies to many fast-track trials. High levels of motivation are necessary to achieve some of the optimization targets and this requires that staff and patients are fully informed of what is expected of them. In an attempt to minimise bias, all potentially ambiguous endpoints were strictly defined prior to commencement of the trial, and a standardised discharge protocol was followed. Morbidity and mortality, need for readmission and the number of GP visits were assessed at one month. Should the decision to discharge patients have been biased, a recordable difference in one or more of these endpoints might have been anticipated.

Randomization resulted in comparable groups, and while the two cohorts did not have exactly similar procedures performed, overall POSSUM operative severity scoring was similar. The only difference noted after randomization was that of lower preoperative grip strength in optimized patients. A possible explanation is that given the large number of outcome measures recorded, a statistical difference in at least one end point would

have been anticipated by chance. Alternatively, this difference may simply be a reflection of an increased absolute number of male patients in the control group.

The individual treatment strategies included in the optimization package were collated following an extensive literature review. Preference was given to treatment strategies known to encourage the return of gut function after surgery. To be included in the multimodal package, treatment parameters had to satisfy a number of criteria. Firstly there had to be good evidence to support their safety and efficacy in colorectal patients. Secondly there had to be some theoretical basis to support their inclusion. Finally they had to be relatively easy to implement, without relying on highly specialised skills, or major financial outlays. The resultant 10-point optimization package summarised in Table 3.1 involved preoperative, peroperative, and postoperative strategies.

Preoperative verbal and written information about the operation and the postoperative rehabilitation programme reduce anxiety, pain, and hospital stay and encourages compliance with the aggressive rehabilitation after surgery (Egbert *et al*., 1964; Hathaway, 1986; Disbrow, Bennett and Owings, 1993; Morrell, 2001; Fearon *et al*., 2005). Probiotics and prebiotics were prescribed in an attempt to beneficially modulate the resident gut microflora, and positively impact on the gut barrier function. The use of synbiotics has been associated with improved healing of colonic anastomoses (Mangiante *et al*., 2001), and decreased post-operative infections following abdominal surgery (Rayes *et al*., 2002). Patients on the optimization arm received preoperative carbohydrate loading together with a shortened preoperative fast of 3 hours as opposed to the

traditional 'nil-by-mouth from midnight' policy. This practice is well documented to be safe (Brady, Kinn and Stuart, 2003), and has repeatedly been shown to improve outcomes of major surgery possibly by decreasing post-operative insulin resistance (Ljungqvist, Nygren and Thorell, 2002). Optimized patients did not receive any form of bowel preparation. Contrary to popular belief, there is no convincing evidence that bowel preparation decreases anastomotic leakage (Guenaga *et al*., 2003; Zmora *et al*., 2003), postoperative septic complications (Guenaga *et al*., 2003; Zmora *et al*., 2003), or improves overall outcomes in this group of patients. On the other hand, it does stress patients and exacerbates preoperative electrolyte imbalances and dehydration, particularly in the elderly and when combined with a prolonged preoperative fast (Beloosesky *et al*., 2003).

During the peroperative period, patients were maintained on high (80%) inspired oxygen concentrations as this has been shown to be safe and may lower the risks of septic wound complications possibly by increasing intestinal intramural oxygenation (Ratnaraj *et al*., 2004) and enhancing oxidative killing by neutrophils (Grief *et al*., 2000). Furthermore, supplemental oxygen probably reduces the incidence of postoperative nausea and vomiting (Grief *et al*., 1999). Transverse abdominal incisions were used in place of vertical (midline or paramedian) ones. Such incisions have been associated with lower postoperative pain scores and subsequent chest infection rates (Grantcharov *et al.*, 2001; Lindgren *et al.*, 2001). Transverse incisions also encourage earlier feeding and ambulation and shortened hospital stay (Donati *et al.*, 2002; Kam *et al.*, 2004). No drains were left at the end of the procedure and NG tubes placed preoperatively were

removed in recovery as repeated studies have failed to show any conclusive benefit in their use (Cheatham *et al.*, 1995; Merad *et al.*, 1999). Furthermore, drains and NG tubes cause distress to patients and limit their postoperative mobilisation (Hoffmann *et al.*, 2001). Postoperatively, patients were allowed fluids *ad libitum* on the day of surgery, and diet was introduced as tolerated following this. Early reintroduction of fluids, oral supplements and diet have been shown to be safe and probably desirable after colorectal procedures, with commensurate improvements in patients' quality of life (Reissman *et al*., 1995; Watters *et al*., 1997; Beier-Holgersen and Boesby, 1998; Beattie *et al*., 2000; Lewis *et al*., 2001). Patients were mobilised from the first postoperative day according to a structured mobilization plan. This is known to decrease postoperative ileus and results in fewer complications of abdominal surgery (Basse *et al*., 2002; Kehlet and Wilmore, 2002).

Opiates were avoided postoperatively in all patients and analgesia was provided via an epidural catheter. Pain relief was standardised in both groups to exclude this as a confounding factor. The administration of regular postoperative opiates is known to increase patient nausea and vomiting and prolong postoperative ileus (Jorgensen *et al*., 2000; Kehlet and Wilmore, 2002; Kehlet and Dahl, 2003; Fearon *et al*., 2005). A few case reports have suggested that continuous infusion of epidural local anaesthetic may lead to an increased incidence of early anastomotic leakage, partly through the stimulatory effect this has on gastrointestinal motility, however this has never been proven in an appropriately powered randomised controlled trial.

Advantages of fast-track surgery noted in this trial are consistent with those of other fast-track trial where epidural analgesia was not standardized between the two arms of the study, suggesting that there is more to the beneficial effects of optimization than that offered by epidural analgesia alone. This trial demonstrates that multimodal optimization is associated with shortened hospital stays. Optimized patients in this trial were hospitalised for a median of 2.5 days less than controls. It has to be stressed however that an earlier discharge from hospital should not be the primary objective of surgical care. Indeed, the principal driving force should be to improve care by decreasing morbidity and mortality associated with treatment while ameliorating overall quality of life; safety remaining one of the major concerns of physicians with regards to fast-track surgery (Kehlet and Wilmore, 2005). Results from this study do not indicate that optimization in any way decreased the level of care, or subjected patients to unnecessary risks because of earlier discharge. Indeed, it may be argued that getting patients home sooner might speed up the rehabilitation process required after major surgery. In addition, and with reference to the issue of safety, patients were reviewed at one month after surgery and there was no increase in complications or readmission rates associated with fast-tracking. Overall hospital stays were shorter for patients on the intervention arm of the study. Further, optimized patients did not need to visit their GP more frequently. It should be noted, however, that this trial was never powered to test these end points, and larger trials will be required for definite conclusions in this respect. However, purely on theoretical grounds, decreased catheterisation, earlier mobilisation, limited time on an intravenous infusion, and shorter hospitalisation would all be expected to be associated with a reduction in postoperative morbidity.

Patients recruited to this trial had a median ASA of 2. This can in part be explained by criteria set down in the study protocol. Only patients living independently at home were recruited so as to avoid delays to post-operative discharge based solely on social factors and unrelated to surgery. Optimization studies by other investigators on colorectal patients with higher average co-morbidities (median ASA of 3-4) have shown similar findings of safety, shorter hospital stays and other improved outcomes (Delaney *et al*., 2001). This suggests that multimodal optimization practices can be implemented safely for all patients, irrespective of extent of surgery or operative risk.

It is commonly assumed that the benefits of multimodal optimization programmes are a consequence of decreased physiological and psychological stresses associated with surgery (Wilmore, 2002). The surgical stress response is mediated via neuroendocrine mechanisms leading to alterations in protein homeostasis (increased catabolism), hypermetabolism, altered carbohydrate metabolism (increased gluconeogenesis and insulin resistance) and increased lipolysis (Weissman, 1990). In the short term, the stress response can be advantageous, but over a longer period it can lead to organ dysfunction, loss of lean body mass, reduced muscle power, and fatigue (Henriksen, 2000). Therefore, measures aimed at curtailing the operative stress response result in the attenuation of postoperative organ dysfunction and result in improved outcomes. Beneficial effects on postoperative cardiac and respiratory function are well documented (Kehlet, 1997; Desborough, 2000). Opiate avoidance, epidural analgesia, and early mobilisation and enteral challenge further decrease postoperative nausea, vomiting and ileus (Baig and Wexner, 2004), leading to an earlier return of gut function (Anderson *et al*, 2003; Kehlet

and Dahl, 2003).

The ten points adopted in this optimization package have, in addition to the benefits previously mentioned, a direct or indirect effect on gut function. Patient information prior to surgery leads to expectations of normal intakes. Preoperative carbohydrate loading is well known to reduce postoperative insulin resistance but is also associated with normalisation of intestinal tolerance (Hausel *et al*., 2005). Avoidance of opiates, judicious use of drains and avoidance of bowel preparation all contribute to preservation of gut function (Kurz and Sessler, 2003; Baig and Wexner, 2004). High inspired oxygen concentrations are known to reduce postoperative nausea and preservation of gut function may be encouraged by use of probiotics. Few would disagree that early mobilisation encourages normalisation of intestinal activity (Mythen, 2005). Results of this trial show that attenuation of postoperative gut failure is not just a result of epidural analgesia and opiate sparing and suggests that earlier return or preservation of gut function may be important to the success of multimodal optimization. In this study, the return of gut function was established by the ability of a patient to tolerate 3 light meals a day. However, the lack of a validated and quantifiable definition of what constitutes adequate as opposed to IGF makes inferences from observations relating to gut function difficult to interpret with accuracy.

The gastrointestinal tract, with its GALT, is the single largest immunological and cytokine producing organ in the body. This structural adaptation to function is vital to the role of the gut as a barrier, protecting the internal milieu from luminal contents, and is

likewise presumably pivotal in orchestrating the stress response to surgery. The gut also has numerous other endocrine and exocrine hormonal functions, along with its role in the digestion and absorption of foodstuffs. It would seem logical, therefore, to propose that the attenuation of transient IF following surgery might be important to the observed benefits of fast-track surgery. This is supported by a number of studies that have demonstrated improved outcomes in association with enteral feed tolerance (DiFronzo *et al*., 2003). Pursuing this rationale, the disadvantages perceived with parenteral nutrition (PN) may occur not as a consequence of the parenteral nutrients but rather because these patients, by definition, do not have a normally functioning gut, necessitating the institution of TPN. An improved understanding of IF and the effects of modulation of gut function by means of customised gut-directed therapies may lead to further improvements in perioperative care. Optimization may represent one way of achieving this. Like other single organ failures, the return of gut function may prove to be an independent indicator of outcome.

3.5 CONCLUSION

Findings from this study confirm the benefits of an optimization programme of perioperative care in patients undergoing colorectal surgery. The evidence suggests but does not prove that maintenance or return to normal of gut function is an essential prerequisite of successful fast-track programmes. Definitive conclusions about the importance of adequate gut function, however, are hindered by the lack of an objective

and validated definition for this end point. Developing such a definition will be the main objective of the next series of studies in this thesis.

CHAPTER 4:

DEFINING ADEQUATE & INADEQUATE GUT FUNCTION

'What cannot be defined cannot be measured,
what cannot be measured cannot be improved,
and what cannot be improved will eventually deteriorate.'

The Quality Axiom
(Anonymous)

4.1 INTRODUCTION: ESTABLISHING THE STATE OF GUT FUNCTION

There is mounting evidence to implicate gut failure in the onset and propagation of disease. and numerous authors have attempted to establish definitions to distinguish adequate gut function from gut failure (Fleming and Remington, 1981; Nightingale, 2001; O'Keefe *et al*, 2006). Much like other single organ failures, the state of gut function, be that adequate or inadequate, has been defined in terms of the organ's primary role, that of nutrition. Unfortunately these established definitions are somewhat generic and unquantifiable. This has made application to daily practice difficult, and comparison of results between clinical studies impossible. For these and other reasons, clinicians still rely on surrogates of gut function (such as the auscultation of bowel sounds or the passage of flatus and faeces) to make functional bedside assessments of the gastrointestinal tract (Baker and Dudley, 1961; Rothnie, Harper and Catchpole, 1963).

These clinical assessments of gut function are all somewhat subjective, and assess functions of the gut other than its primary role as an organ of nutrition. In contradistinction, the various attempts at defining gut failure in the literature appear to have a common theme; namely that the gastrointestinal tract can be said to be functioning appropriately when it is able to tolerate adequate dietary intake to satisfy an individual's nutritional requirements and without the need for intravenous supplementation (Jeejeebhoy, 2005). Anything less than this and the gut is lacking in its primary role, which by definition represents a state of gut failure. To be of use in daily clinical practice, however, a definition also needs to be quantifiable, objective, reproducible, pragmatic

and easily applicable by the bedside. In addition, a degree of evidence base to relate it to outcome is desireable.

The overarching aim of this chapter is to establish the best test which can be used as a definition for adequate gut function. This definition will be based on the tolerance by the gut of an appropriate oral and/or enteral challenge over a suitable period of time and attempts will be made to relate this to patient outcome. A stepwise methodology will be pursued, firstly to establish what is meant by 'an appropriate oral and/or enteral challenge', and secondly to ascertain what is 'a suitable period of time' to be able to make this assessment (i.e. how much needs to be tolerated by the gut and over what period of time). Preliminary work will be required to establish the percentage of a patient's nutritional requirements that needs to be tolerated by the gut to affect prognosis. A subsequent study will then establish 'the time period necessary' to be able to make the assessment of the state of gut function by once again relating this to patient outcome.

4.2 PRELIMINARY WORK: A REANALYSIS OF PUBLISHED DATA

Data previously collected by other members of the Combined Gastroenterology Research Unit was re-interrogated retrospectively. This data had been compiled prospectively by other investigators as part of a study of all patients aged 18 years or over who required adjuvant nutritional support at Scarborough Hospital between November 1995 and July 1999. Results from this dataset have been published previously (Woodcock *et al*., 2001).

The author of this thesis reanalysed a subset of this data in a novel way so as to attempt to define the term 'adequate nutrition' by relating the enteral tolerance of ≥70, ≥80, and ≥90 per cent of patients' calculated nutritional requirements to outcome. The primary end-point of this reanalysis was in-patient survival.

From the original database of 562 individuals, a subgroup of 276 consecutive patients receiving variable amounts of EN was identified. Data pertaining to these 276 patients was collated to include all patient demographics, nutritional parameters of weight, height, BMI, and concomitant TPN administration. The length and adequacy of enteral feeding, the length of hospital stay, as well as the need for ICU admission were also recorded. Oral intakes were recorded by means of food charts and diet diaries, and the energy values for this intake were calculated by dieticians and added to the tolerance of the prescribed feed. The overall adequacy of feeding was expressed as a percentage of the total volume of feed prescribed. The delivery of ≥70, ≥80 and ≥90 per cent of these requirements via the enteral route was recorded in a categorical fashion and each was then associated with in-patient survival or mortality.

Serum albumin was evaluated as an assessment of the acute phase response, and to permit the evaluation of nutritional status using the nutritional risk index (NRI; Baker *et al*., 1982) which was calculated according to the equation (1.519 x serum albumin) + (0.417 x % usual body weight). A physiological score was also calculated using the POSSUM scoring system (Copeland *et al*., 1991) according to parameters measured at the time of commencement of feeding. In the context of the present reanalysis, POSSUM scores

were used as a guide to severity of illness.

The site and development of septic complications had been prospectively verified and recorded at the time of original data collection. For purposes of this study, septic morbidity was defined as the presence of recognized pathogens in body tissues that are normally sterile, confirmed by the results of culture and supported by clinical, radiological, or haematological evidence of infection. All septic complications occurring between the time of commencement of nutritional support and discharge from hospital had been recorded

Nutritional requirements were calculated by senior dieticians according to the Schofield method, to provide target intakes of approximately 30 kcal kg^{-1} d^{-1} non-protein energy and of approximately 9 gN/d protein. This load was then administered using a commercially available polymeric feed (Osmolite®, Abbott Laboratories Ltd., Kent, UK) whose constituents are summarised in appendix 5. The initial rate of delivery was full strength feed at 30 mL/h, increasing stepwise to full intake over a period of 24–48 hours according to patient tolerance. During this build-up period, tubes were aspirated every 6 hours. If less than 100 mL was aspirated, the aspirate was replaced and feeding continued, whereas if the volume of aspirate exceeded 100 mL, the aspirate was not replaced and the feed slowed or stopped temporarily in accordance with the local feeding protocol at the time of the original collection of data.

4.2.1 Statistical analysis

Results were tabulated on an Excel® spreadsheet (Excel for Windows®, Microsoft Corporation, Redmond, Washington, USA) and then analysed using SPSS® for Windows® version 11.5 (SPSS®, Chicago, Illinois, USA). All parametric data were expressed as means (SD) and nonparametric data as medians (IQR). Comparisons between groups were made using Mann-Whitney U test for non-parametric quantitative data. Qualitative data was assessed using χ^2 test or Fischer's exact test for small cohorts as appropriate. The association between outcome and the delivery of $\geq$70, $\geq$80 and $\geq$90 per cent of nutritional requirements was assessed using χ^2 test. Values that were significant on univariate analysis were then assessed for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), the number needed to diagnose (NND; calculated as $^{1}/_{[\text{sensitivity} -(1\text{-specificity})]}$) and the number needed to treat (NNT; calculated as $^{1}/_{\text{difference in proportions}}$) . 95 per cent confidence intervals (C.I.) for these variables were also calculated. A p-value of less than 0.05 was taken to signify a statistically significant difference. A sample size calculation was not possible as there was no data in the literature to refer to.

4.2.2 Results from the data reanalysis

Demographic data and other characteristics for the 276 patients in this reanalysis are summarised in Table 4.1. A total of 202 (75%), 175 (63%) and 114 (41%) patients

respectively tolerated ≥70, ≥80 and ≥90 per cent of their calculated nutritional requirements enterally. One hundred and ten (40%) patients developed evidence of sepsis at one or more sites with a total of 137 septic episodes being recorded. These are summarised in Table 4.2. One hundred and four (38%) patients died during their hospital stay.

Enteral tolerance of < or ≥70 per cent of calculated nutritional requirements was not associated with in-patient outcome (p=0.086) and was therefore excluded from further statistical analysis. Outcome was associated with both 80 per cent (p=0.021) and 90 per cent (p=0.045) values of enteral tolerance. Values for specificities, sensitivities, PPV, PNV, NND and NNT together with relevant 95% C.I. for each are summarised in Table 4.3.

The enteral tolerance of ≥80% of nutritional requirements was associated with a better sensitivity to in-patient survival than ≥90% but the specificity was lower. Corresponding PPV and NPV values were comparable for the two values, but the NND for ≥80% was 7.162 when compared to 8.146 for ≥90%. Similarly the NNT values were respectively 7.248 as compared to 8.410. Sixty three per cent of patients managed to achieve ≥80% tolerance when compared to only 41% who managed to achieve ≥90%.

Using the cut-off value of 80% tolerance, there was no difference in the length of hospital stay for patients who tolerated <80% of the prescribed nutrition when compared to those who tolerated ≥80% (respectively 23.5 (12-37) days *versus* 26.5 (15-45) days; p=0.105).

Factor	Value
Total number of patients	276
Age (years) *	70 (56-76)
Sex	
Male	163 (59%)
Female	113 (41%)
% enteral feed administered	
70%	202 (73%)
80%	175 (63%)
90%	114 (41%)
Admitted to ICU	144 (52%)
BMI *	23 (20-26)
Length of feeding (days) *	7 (3-15)
Receiving concomitant TPN	
Yes	56 (20%)
No	220 (80%)
NRI *	86.6 (79.8-94.9)
Serum albumin (g/L) *	32 (27-36)
Patients with septic complications (%)	110 (40%)
POSSUM physiological score *	26 (21-34)
In-hospital death (%)	104 (38%)

Table 4.1: Demography, nutritional parameters and outcome for data reanalysis. Interpretation of NRI according to Baker *et al*. (1982): well nourished (score > 98.5), mildly/moderately malnourished (83.5 – 98.5), severely malnourished (score < 83.5). * median (IQR) values; NRI, nutrition at risk score; ICU, intensive care unit; BMI, body mass index.

Complication	Number of patients (%)
Septic complications	110 (40)
Chest infections / aspiration pneumonia	52 (19)
Urinary tract infections	29 (11)
Delivery site infection (PEG, PEGJ, CVP)	24 (9)
Wound infections	20 (7)
Abdominal collections	4 (1)
Septicaemia / Septic shock	4 (1)
Other	4 (1)
In hospital death	104 (38)

Table 4.2: A list of complications in all 276 patients. There were a total of 137 septic episodes in 110 patients who manifested septic complications.

Variable	Tolerance of ≥80%	Tolerance of ≥90%
Patients (%)	175 (63)	114 (41)
Survival (%)	118 (67)	79 (69)
Deaths (%)	57 (33)	35 (31)
Sensitivity (95% C.I.)	0.686 (0.642, 0.730)	0.459 (0.414, 0.502)
Specificity (95% C.I.)	0.452 (0.379, 0.524)	0.663 (0.589, 0.733)
PPV (95% CI)	0.674 (0.631, 0.717)	0.693 (0.625, 0.757)
NPV (95% CI)	0.465 (0.390, 0.540)	0.426 (0.378, 0.471)
NND (95% CI)	7.162 (3.891, 48.444)	8.146 (4.253, 342.221)
NNT (95% CI)	7.248 (3.938, 49.028)	8.410 (4.391, 353.307)
P-value	0.021	0.045

Table 4.3: Association between survival and the tolerance of ≥80% or ≥90% of nutritional requirements. The p-values quoted relate to the association of the enteral tolerance of ≥80% or ≥90% of calculated nutritional requirements with survival.

4.2.3 Interim conclusion

The results of this reanalysis from a large cohort of patients receiving EN suggest that the best test for gut function may be represented by the cut off of ≥80% enteral tolerance of calculated nutritional requirements. This observation is based on better sensitivity values and NPV for outcome, together with improved NND and NNT values and the fact that more than 60% managed to achieve ≥80% tolerance when compared to only 41% managing to achieve ≥90%.

The inference from this preliminary work is that a surrogate marker for the state of gut failure in an individual patient can be represented by the enteral tolerance of less than 80% of their calculated nutritional requirements. However, in view of a number of inadequacies of the dataset from the Woodcock study (as discussed later in section 4.4), it was necessary to embark on a second study with the primary aim of establishing a time scale over which the assessment of enteral tolerance would be made (i.e. to establish the period of time over which patients need to tolerate less than or ≥80% of calculated nutritional requirements to manifest gut failure or adequate gut function).

4.3 A PROSPECTIVE AUDIT TO ESTABLISH A DEFINITION OF GUT FAILURE

The previous analysis establishes an evidence-base for defining the adequacy of EN in

terms of the ability of a patient to tolerate ≥80 per cent of their calculated nutritional requirements via the oral or enteral route. Tolerance of less than this value may be associated with a poorer outcome, and therefore indicates failure of the gut. However, to be comparable and reproducible, clinical assessments need to be carried out over a fixed period of time, measured in hours, days or multiples thereof.

For this reason, the aim of this observational study was to establish the period of tolerance necessary to be able to make assessments on the state of gut function. In other words, this study endeavours to answer the question of how long a patient needs to tolerate ≥80% of their calculated nutritional requirements to be deemed to have adequate gut function (or in its absence, gut failure). Enteral tolerance of < or ≥80 percent of nutritional requirements for various time periods (≥24, ≥48 and ≥72 hours) were associated with outcome.

4.3.1 Patients and methods

Data was collected prospectively from 100 consecutive patients requiring EN at Scarborough Hospital. Patients were followed up for the duration of their hospital stay. In addition, mortality data was collected for a total period of 6 months from the instigation of oral/enteral feeding. The primary end point of this study was mortality at 6 months (180 days). This mortality data was then associated with the enteral tolerance of ≥80 percent of calculated nutritional requirements over a minimum continuous period of 24,

48 and 72 hours. Tolerance to oral or enteral feeding was recorded on a regular basis for the duration of hospital stay.

Nutritional requirements were calculated by senior dieticians according to the Schofield method (Todorovic and Micklewright, 2004; appendix 4), to provide target intakes of 20-25 kcal kg^{-1} d^{-1} non-protein energy and of approximately 0.17g N kg^{-1} d^{-1}. This load was administered using a standardized commercially available polymeric feed (Osmolite, Abbott Laboratories Ltd., Kent, UK) whose constituents are summarised in appendix 5. Enteral feed tolerance was tabulated on an hourly basis on patients' fluid balance charts for the duration of feeding. Oral intake was recorded by means of food charts and diet diaries for the duration of hospital stay. The nutritional values for oral intake were calculated by dieticians and then added to the values of enteral feed tolerance to permit an estimate of overall enteral tolerance by individual patients. The maximum continuous period of tolerance of $\geq$80 per cent of calculated nutritional requirements was measured to establish whether this was $\geq$24, $\geq$48 or $\geq$72 hours. An example how gut function or failure was assessed is represented graphically in Figure 4.1.

As mentioned previously, the primary outcome measure for this second study was mortality at 180 days from the commencement of feeding. This data was ascertained by means of the hospital's computerised Patient Administration System for patients who died in Scarborough Hospital. Further information was gathered by contacting patients' GP's and/or the patients or their relatives by telephone.

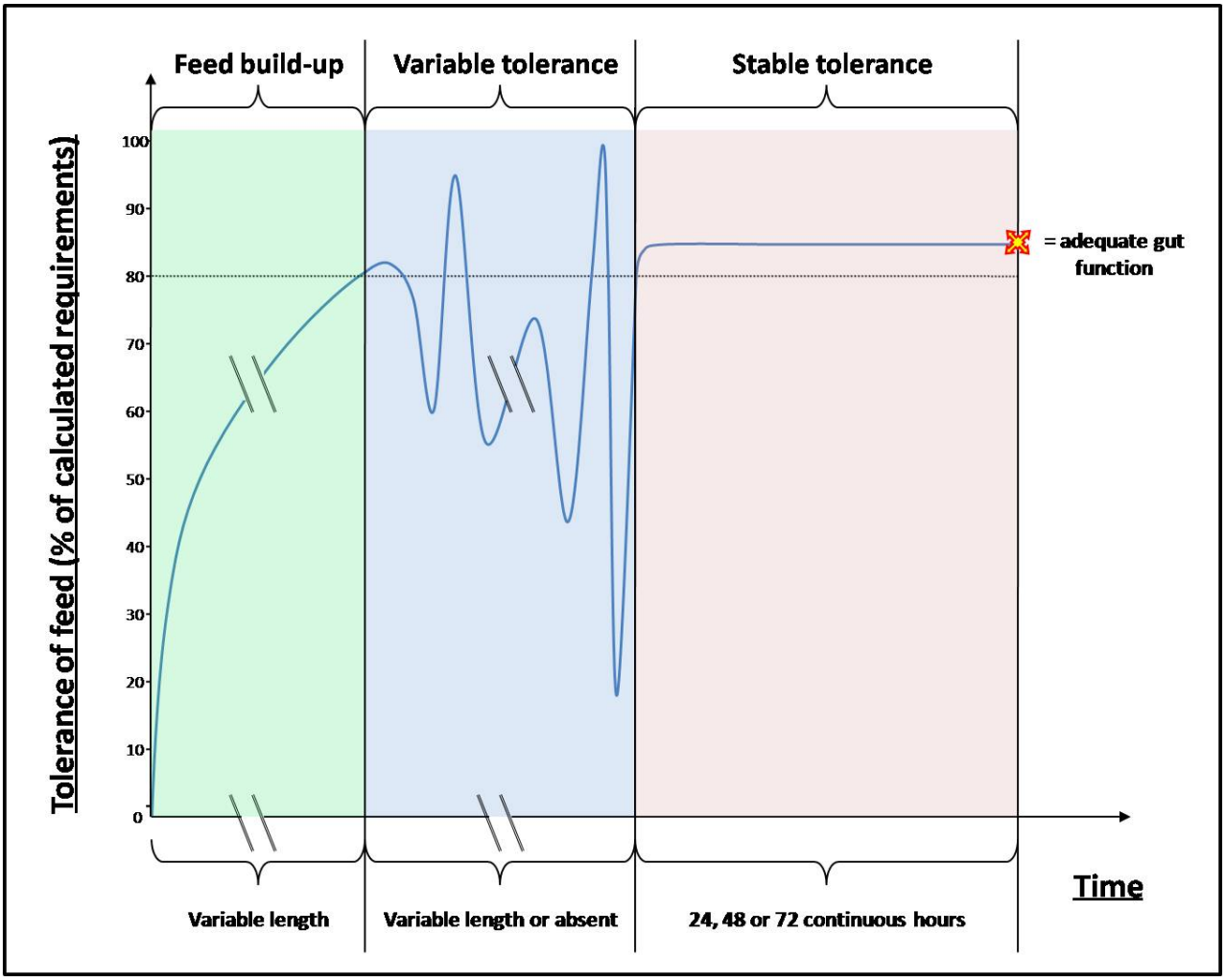


Figure 4.1: Method of assessing the state of gut function by incorporating the element of time. Assessment was started at the commencement of enteral feeding and included a cumulative period of feed build-up (dictated by standardized institutional feeding protocols), a period of variable tolerance (which may or may not have been present depending on individual feed tolerance) together with a sustained tolerance of a minimum of 80% of calculated nutritional requirements for at least 24, 48 or 72 hours. Patients were deemed to have adequate gut function or gut failure respectively by whether or not they achieved the point indicated by an asterisk for the appropriate length of time.

Other data points recorded during hospital stay included patient demographics, nutritional requirements and nutritional parameters of height, weight, BMI, and concomitant TPN administration. The length of adjuvant feeding was recorded and the appropriateness of enteral support was assessed by a minimum of five days of adjuvant nutrition (anything less than 5 days administration was deemed as inappropriate instigation of adjuvant feeding). The need for surgery or ICU admission and the length of hospital stay were recorded. Disease severity was assessed using APACHE (Acute physiological and chronic health evaluation) II scores according to parameters measured at the time of commencement of adjuvant feeding.

All complications were noted as was the development of SIRS. Morbidity was grouped into feed related, delivery related or septic complications. For purposes of this study, septic morbidity was defined as the presence of recognized pathogens in body tissues that are normally sterile, confirmed by the results of culture and supported by clinical, radiological, or haematological evidence of infection. Data for this study was collected by the author of this thesis together with other members of the multidisciplinary nutrition team at Scarborough Hospital.

4.3.2 Statistical analysis

Results were tabulated on an Excel® spreadsheet (Excel for Windows®, Microsoft Corporation, Redmond, Washington, USA) and then analysed using SPSS® for

Windows® version 11.5 (SPSS®, Chicago, Illinois, USA). All parametric data were expressed as means (SD) and nonparametric data as medians (IQR). Comparisons between groups were made using Student's *t*-test or Mann-Whitney *U* test for quantitative data as appropriate. Qualitative data was assessed using the χ^2 test or Fisher's exact test for small cohorts. A p-value of less than 0.05 was considered to signify a statistically significant difference.

The association between the delivery of ≥80 per cent of nutritional requirements for ≥24, ≥48 or ≥72 hours and outcome at 180 days was investigated. Values that were significant on univariate analysis were then assessed for sensitivity, specificity, PPV, NPV, the number needed to diagnose (NND; calculated as $^{1}/_{[\text{sensitivity} -(1\text{-specificity})]}$) and the number needed to treat (NNT; calculated as $^{1}/_{\text{difference in proportions}}$). 95 per cent confidence intervals (C.I.) for these variables were also presented. Once again, there was no data in the literature to permit a prospective sample size calculation based on the effects of the state of gut function on outcome.

4.3.3 Results from the prospective audit

A total of 100 patients (M:F = 64:36; median age 66 (49-76) years) were audited. Demographic data and other characteristics for these patients are summarised in Table 4.4. A total of 89 (89%), 85 (85%) and 81 (81%) patients tolerated ≥80 per cent of their calculated nutritional requirements for ≥24, ≥48, and ≥72 hours respectively. Thirty eight

Factor	Value
Total number of patients	100
Age *	66 (49-76)
Sex	
Male	64 (64%)
Female	36 (36%)
Admitted to ICU	78 (78%)
Needed surgery	45 (45%)
BMI *	24 (21-31)
Nutritional requirements (kcal/day) *	1595 (1424-1860)
Length of feeding (days) *	10 (6-19)
Less than 5 days of feeding	18 (18%)
Patients tolerating adequate nutrition (≥80%) for:	
≥ 24 hours	89 (89%)
≥ 48 hours	85 (85%)
≥ 72 hours	81 (81%)
Receiving concomitant TPN	32 (32%)
Complications	
Any	54 (54%)
Septic	43 (43%)
Feed related	34 (34%)
Related to the delivery system	24 (24%)
SIRS / Sepsis syndrome	66 (66%)
APACHE II score *	13 (8-18)
Death by 180 days	38 (38%)

Table 4.4: Patient demography, nutritional parameters and outcome.

(* median (IQR) values)

(38%) patients died during the first six months of follow. During their hospital stay, a total of 54 (54%) patients developed evidence of one or more complications (34 (34%) patients developed feed related morbidity, 24 (24%) developed delivery system related problems, and 43 (43%) developed septic complications).

Enteral tolerance of $\geq$80 per cent of calculated nutritional requirements for $\geq$24, $\geq$48, and $\geq$72 hours were all associated with outcome at 180 days (respectively $p=0.005$, $p<0.001$, $p=0.001$) and were all included for further statistical analysis. Values for specificities, sensitivities, PPV, PNV, NND and NNT together with relevant 95% C.I. for each are summarised in Table 4.5. The tolerance of $\geq$80% of calculated nutritional requirements for a continuous period of $\geq$48 hours was considered to represent the optimal balance between these variables and outcome. This was utilized as the best test to determine adequacy of gut function. Any level of enteral tolerance less than this value represented a state of gut failure.

Using this definition, a total of 15 (15%) patients showed evidence of gut failure. These patients were then compared to patients that manifested adequate gastrointestinal function. Increased age (78.4 (65.7 – 82.1) *versus* 64.4 (44.8 – 74.8) years; $p=0.015$), a curtailed period of adjuvant feeding (5 (2 – 10) *versus* 11 (7 – 20) days; $p=0.003$) and a higher APACHE II score (19 (14 – 26) *versus* 12 (7 – 17) days; $p=0.008$) were all associated with the presence of gut failure on univariate analysis. Patients with gut failure were noted to have lower nutritional requirements but this did not achieve significance

Variable	Tolerance for ≥24 hours	Tolerance for ≥48 hours	Tolerance for ≥72 hours
Patients (%)	89 (89%)	85 (85%)	81 (81%)
Sensitivity (95% CI)	0.968 (0.919, 0.991)	0.968 (0.914, 0.991)	0.919 (0.858, 0.962)
Specificity (95% CI)	0.237 (0.157, 0.274)	0.342 (0.254, 0.380)	0.368 (0.269, 0.438)
PPV (95% CI)	0.674 (0.640, 0.690)	0.706 (0.667, 0.723)	0.704 (0.657, 0.736)
NPV (95% CI)	0.818 (0.542, 0.948)	0.867 (0.644, 0.962)	0.737 (0.537, 0.876)
NND (95% CI)	4.888 (3.772, 13.256)	3.227 (2.699, 5.995)	3.475 (2.499, 7.898)
NNT (95% CI)	2.031 (1.567, 5.508)	1.747 (1.461, 3.223)	2.270 (1.633, 5.159)
P-value	0.005	<0.001	0.001

Table 4.5: Association between survival and the tolerance of ≥80% of nutritional requirements for at least 24, 48 or 72 hours.

(p=0.077). Gastrointestinal insufficiency was associated with a higher mortality at 180 days (13/15 (87%) patients *versus* 25/85 (25 %) patients; p<0.001). Other comparisons between the groups are summarised in Table 4.6.

4.4 DISCUSSION: ESTABLISHING THE STATE OF GUT FUNCTION

The collective results of these two studies demonstrate that adequate gut function can be associated with outcome by defining it quantitatively in terms of the tolerance to an oral or enteral diet. When a patient's gut tolerates 80 per cent or more of their calculated nutritional requirements for a minimum continuous period of 48 hours, they appear to have a better outcome and therefore this cut-off may demonstrate a state of adequate gut function. Similarly, the enteral tolerance of anything less than this cut-off represents a state of gut failure. Patients that manifest an adequately functioning gastrointestinal tract appear to have a better prognosis than patients with gut dysfunction.

There are two possible explanations for these data; either the additional calories or nitrogen received by these patients actually influenced outcome, or, tolerance to 80% of calculated nutritional requirements for a minimum period of 48 hours represents a surrogate measure of gut function, which includes all aspects of gastrointestinal function not just digestive processes. We consider it improbable that the provision of a few additional calories or grams of nitrogen alone could have accounted for these results. Numerous studies over many years have consistently failed to demonstrate changes in

Factor	Normal gut function	Gut failure	P-value
Patients	85	15	–
Age (years) *	64.4 (44.8 – 74.8)	78.4 (65.7 – 82.1)	**0.015**
Sex			0.100 ‡
Male	54 (64%)	10 (67%)	
Female	31 (36%)	5 (33%)	
Admitted to ICU	66 (78%)	12 (80%)	1.000 ‡
Needed surgery	40 (47%)	5 (33%)	0.461 ‡
BMI *	24.7 (21.0 – 30.7)	26.1 (21.8 – 34.1)	0.511
Nutritional requirements (kcal/day) *	1610 (1431 – 1869)	1500 (1381 – 1693)	0.077
Length of feeding (days) *	11 (7 – 20)	5 (2 – 10)	**0.003**
Less than 5 days of feeding	11 (13%)	7 (47%)	**0.002**
Receiving concomitant TPN	25 (29%)	7 (47%)	0.187
Complications			
Any	47 (55%)	11 (73%)	0.331
Septic	36 (42%)	7 (47%)	0.755
Feed related	27 (32%)	7 (47%)	0.275
Related to the delivery system	20 (24%)	4 (27%)	1.000 ‡
APACHE II score *	12 (7 – 17)	19 (14 – 26)	**0.008**
Length of hospital stay (days) *	26 (16 – 39)	15 (10 – 29)	**0.015**
Death by 180 days	25 (29%)	13 (87%)	**<0.001**
Time to death (days) *	19 (11 – 53)	8 (5 – 15)	**0.006**

Table 4.6: Comparison of patients exhibiting normal gut function with those manifesting gut failure.

(* median (IQR) values; ‡ Fischer's exact test)

outcome with nutritional support. The suggestion, therefore, is that tolerance to 80% or more of nutritional requirements for a minimum continuous period of 48 hours is a surrogate marker of gut function and may relate to patient outcome.

Given its many homeostatic roles, it has long been hypothesised that gastrointestinal insufficiency may act as a 'motor of multiorgan failure, ultimately resulting in death (Marshall, Christou and Meakins, 1993; Nieuwenhuijzen, Deitch and Goris, 1996; MacFie, 2000; Ding and Li, 2003). There is a wealth of circumstantial evidence that supports this (MacFie, 2000; Magnotti and Deitch, 2005; Deitch, Xu and Kaise, 2006; MacFie *et al*., 2006; Reddy *et al*., 2007), and the results from the two studies presented here accord with the theoretical principles of the 'gut origin of sepsis hypothesis'. Our findings demonstrate that as predicted by this hypothesis, gut dysfunction was associated with poorer outcomes.

The group of patients receiving EN were ideal to study because all were being seen regularly by dieticians, had nutritional requirement estimations performed, and had their calorific intake accurately recorded as part of their daily clinical care. It is well reported that few patients fed by the enteral route actually achieve all their nutritional requirements (Woodcock *et al*., 2001; Mentec *et al*., 2001, Kreymann *et al*., 2006). For this reason, adopting a cut-off tolerance valve of 100% of nutritional requirements to indicate adequate gut function would have been unrealistic. The results of the initial data reanalysis suggest that the tolerance of 80% of estimated requirements demonstrated the best association with outcome (Table 4.3). Results from the subsequent observational

study on 100 patients indicated that this assessment of tolerance of 80% of calculated requirements is best made once a minimum of 48 hours of continuous feeding has elapsed as this is most predictive of outcome (Table 4.5). Characterising gut performance in this way is an innovative approach on the accepted clinical concept of enteral tolerance. There was no supporting evidence in the literature to permit accurate sample size estimations. Additionally, the author recognises a few contentious issues in the methodology applied.

Firstly, there are methodological differences between the initial data reanalysis and the subsequent study. This related primarily to inadequacies of the data from the study by Woodcock (2001). Interpretation of the data from the initial study was complicated by the use of in-patient mortality as opposed to mortality over a fixed time interval from the commencement of feeding. This resulted in a variable period of follow-up between the individuals in this study based on their in-patient length of stay, even though overall this difference did not achieve statistical significance between the groups. This issue was addressed in the subsequent study where a fixed period of follow-up was integral to the methodology. Secondly, physiological POSSUM scoring was used to assess disease severity in the initial reanalysis of data (Copeland, Jones and Walters, 1991). Its relevance for patients other than those undergoing surgery is questionable, but there currently exists no scoring system specifically validated for patients receiving adjuvant nutritional support. A more generic scoring system such as APACHE II would have possibly been more appropriate, but the data reanalysis was a retrospective exercise and as such was limited by the data that had already been collated. However, to address this

concern, APACHE II was incorporated in the subsequent study.

A third issue relates to the method employed in calculating patients' nutritional demands. There are many formulas in the literature to estimate these requirements (Harris and Benedict, 1919; Kleiber, 1932; Fleisch, 1951; Robertson and Reid, 1952; World Health Organization, 1985; Schofield 1985), and it is contentious whether one method is better than another. In addition, the equations necessary for these calculations undergo periodic modification as new data becomes available. The Schofield method was used in the data reanalysis. This established non-protein energy requirements of approximately 30 kcal kg^{-1} day^{-1}. While this was acceptable during the time of original data collection (1995-1999), many would now consider this as predisposing patients to slight overfeeding. For this reason, the modified Schofield equation was used in the subsequent study (Todorovic and Micklewright, 2004). This provided target intakes of 20-25 kcal kg^{-1} d^{-1} non-protein energy. The authors do not envisage this difference to have had significant effects on the results between the two studies. With the inclusion of specified time periods of $\geq$1, $\geq$2 or $\geq$3 days (i.e. $\geq$24, $\geq$48 and $\geq$72 hours), one noticed enhanced robustness of the test for gut failure as evident from the improved sensitivity, PPV, NPV, NND and NNT results. This is despite the fact that the prevalence of gut failure dropped from 38% in the initial data reanalysis to 15% in the subsequent study. The relevance of this change in prevalence lies in the fact that for any diagnostic test, the PPV will be expected to fall as the prevalence of the disease falls while the NPV will rise simply by virtue of the change in prevalence of the condition in the index population (Loong, 2003). The fact that the robustness of the test for gut failure improved despite more than halving its prevalence in the described

study justifies the inclusion of a fixed time period of assessment and substantiates the argument that the changes resulting from the adoption of the updated Schofield formula were at worst inconsequential, and at best beneficial to the final test of gut function. Indirect calorimetry has its advocates as a more accurate alternative to estimate nutritional requirement when compared to the use of formulae such as the Schofield equation (Schebendach *et al*., 1995; Kan *et al*., 2003), but even calorimetry has its problems. The necessary equipment is not widely available, it necessitates specialized expertise for equipment calibration and data interpretation, and it estimates energy expenditure not requirements, even though many consider these to be equivalent. The desire to create a pragmatic definition which could be easily and widely applicable to daily clinical practice precluded the use of calorimetry.

A final limitation of the methodology imployed relates to the supply of what is perceived as representing adequate nutrition. By definition, this implies the provision of sufficient macronutrients (carbohydrates, fats and proteins to supply non-protein energy, together with a nitrogenous load) micronutrients (including vitamins, minerals and other trace elements), and hydrating fluids (water) (Jeejeebhoy, 2005). The requirements of each varies non-linearly in relation to the others, meaning that by using fixed preparation commercially available feeds it is not always possible to provide adequate levels of each without running the risks of under- or overfeeding with other macro- or micronutrients. Since calculations of nutritional requirements primarily relate to non-protein energy estimations, these studies refer to this value when reference is made to $\geq$80 per cent of nutritional requirements. Had these calculations been based on providing adequate

nitrogenous loads, this would have often resulted in non-protein energy overfeeding with all its associated risks.

While it is possible to find a number of perceived deficiencies in the methodology employed in these two studies, there is currently no other quantifiable description in the literature for distinguishing patients with normal gut function from those with gut failure. In other words, there is no yardstick to compare the established definition to. It may be argued, therefore, that given this situation, any arbitrary description to define the state of gut function would have sufficed. The author is however of the opinion that, within their limitations, these studies offer the best possible evidence-base for the classification of gut function and failure. This is achieved by establishing a relationship between the degree of gastrointestinal performance and patient outcome by making use of the surrogate measure of enteral tolerance. It is one possible method (Rombleau and Takala, 1997), but surely not the only conceivable one, to ascertain the state of gut failure and it would be reasonable to assume that alternatives approaches to define the adequacy or otherwise of gut function may also exist.

The two studies accomplish their primary aim by establishing a pragmatic definition for the adequacy or failure of gut function. This was achieved by associating enteral tolerance to outcome. Results from these studies suggest that gut failure is positively associated with age, a higher APACHE II score, and death by 6 months, while being negatively associated with the length of feeding and hospital stay. Neither the APACHE II scoring system nor the sequential organ failure assessment (SOFA) score (nor any

other known scoring system relating to patient outcome for that matter) consider factors relating to nutrition or gut function. This is despite their regular application in daily clinical practice for assessing patients' organ dysfunction as a method of predicting their chances of survival. Whilst this corroborates the notion that the state of gut function is not recognized to be important to the outcome of patients, data from this study cannot explain the higher APACHE II scores in patients with gut failure. Whether this is a result of gut failure or conversely a result of more severe co-morbidity which then brings about attenuation of gut function remains to be determined, but supports the contention that gut failure and ill health are associated. Given the many factors that impact on patient outcome, it is difficult to judge the independent relevance of these associations and their cause or effect relationships with gut failure. To this end, a larger number of patients and a wider breadth of recorded variables and outcome measures would be necessary to perform a reliable multivariate analysis.

4.5 CONCLUSION: ESTABLISHING THE STATE OF GUT FUNCTION

In conclusion, the results of these two studies suggests that normal gut function can be defined by the oral/enteral tolerance of $\geq$80% of calculated nutritional requirements for a continuous period of $\geq$48 hours. By design, this definition of adequate gut function is associated with a favourable outcome. Anything less is a manifestation of attenuated gastrointestinal performance, and represents a state of gut failure. In a similar fashion, gut failure is associated with a poorer prognosis. Enteral tolerance is a good surrogate marker

for gut function or failure.

Alternative approaches to define the adequacy of gut function that do not necessitate the measurement of enteral tolerance probably exist but remain to be investigated and validated. Patients with gut failure appear to have a poorer prognosis when compared to patients with adequate gut function, however this definition needs to be prospectively evaluated. Additionally, it is axiomatic that association does not prove causation. Numerous factors are known to affect patient outcome, and results from these studies suggest that the state of gut function may be one such prognostic factor. It remains to be seen whether the state of gut function is 'independently' associated with patient outcome. As a natural progression from these results, investigating the possible independent association of gut function with outcome will be the main focus of future studies.

CHAPTER 5:

VALIDATING THE DEFINITION OF ADEQUATE GUT FUNCTION AND GUT FAILURE: A MULTIVARIATE ANALYSIS

'From the gut comes the strut,
and where hunger reigns, strength abstains.'

Francois Rabelais
French Clergyman, 1493-1553

5.1 INTRODUCTION: VALIDATING A DEFINITION OF GUT FAILURE

Numerous factors influence patients' prognosis. These include patient characteristics such as age, indicators of organ insufficiency, as well as other signs of disease or sepsis. However, despite its central role in many homeostatic mechanisms, the state of gut function is not recognised to be one of these factors, possibly because:

> "traditional teachings…have promoted the dogma that the gut is dormant, metabolically inactive, and of little physiologic and pathologic significance." (Rombeau and Takala, 1997)

Another possible explanation is the absence of an accepted definition for what constitutes adequate gut function, and what therefore constitutes a state of gut failure. As shown previously (chapter 4) it may be possible to define adequate gastrointestinal function in terms of the tolerance to an enteral challenge. Having established a working definition to distinguish adequate from IGF, and given the many factors that may affect patient outcome, this study was set up to assess whether gut failure is 'independently' associated with patient prognosis. A subsidiary aim was to determine those factors independently associated with gut failure.

5.2 PATIENTS AND METHODS

For purposes of this study, an audit tool for the multidisciplinary nutrition team at

Scarborough Hospital was designed and instigated by the author of this thesis to permit a wide range of data to be recorded. This took the form of a database on an Excel® spreadsheet (Excel for Windows®, Microsoft Corporation, Redmond, Washington, USA) which was stored on the hospital computer systems and was accessible by all members of the multidisciplinary nutrition team through personalised login names and passwords. The author acted as database manager, inputted most of the data, validated all the data stored on the database, and performed all the data analysis.The author of this thesis was also responsible for training the members of the team to ensure uniformity of data recording.

Individual variables recorded were strictly defined prior to commencing the audit period to ensure homogeneous data collection. This was further reinforced by a list of rules which established how each variable was to be recorded. These rules were decided prior to commencing data collection, and were then documented on an interactive key which was write-protected and then saved on the database itself. To further facilitate uniform data recording, formulae and algorithms were integrated into the database where possible. Free text fields were also included to maximise the extent of data collection.

Using this database, data was collected prospectively from 315 consecutive patients requiring adjuvant nutritional support at Scarborough Hospital between January 2005 and September 2006. The point of entry into the study was the day of initiation of inpatient feeding and data was recorded regularly by the author and other members of the nutrition team. Patients were followed up for the duration of their hospital stay. Mortality data was

collected for a total period of 6 months (180 days) from the instigation of feeding.

A large number of variables were prospectively recorded for each patient, and are summarised in Table 5.1. The data collected related to patient demographics, hospital stay, any relevant operative details, the severity of illness, and complications that developed during hospitalization. Evidence of single organ failures was logged, as were a number of nutritional parameters and mortality data.

The primary outcome measure of this study was mortality in the first 180 days. This data was collected as a continuous variable from the commencement of adjuvant feeding and was ascertained by means of in-patient follow-up. The hospital's computerised 'Patient Administration System' was interrogated for patients who died after discharge. Further information was gathered by contacting GP's and/or patients' relatives by telephone. The cause of death was ascertained from death certificates.

Patients had their height recorded and their weight assessed prior to the instigation of feeding. Their weight was re-evaluated regularly thereafter using appropriately calibrated sitting scales or weighing beds. Periodicity of weight measurements was tailored to the patient depending on the individual's clinical condition, but as a minimum this measurement was recorded once weekly. Weight in the previous six months was ascertained from hospital and GP records or from patient recollection when this had not been previous documented (Todorovic *et al*., 2003). Weight changes during the period of illness were calculated, and BMI at the start of feeding was recorded. These

Variables			
Demographics	**Nutritional data**	**Evidence of organ failure**	**Complications**
Age	Weight	Cardiac	Septic
Sex	Weight prior to illness	Respiratory	Tube related
Height	Weight change	Renal	Feed related
	BMI	Hepatic	
	Nutritional requirements	Neurological	
Hospital stay	Reason for feeding	Haematological	**Mortality Data**
	Length of feeding	Gut	
Total length of stay	<5 days feeding		Death in first 6 months
Need for ICU admission	Length of TPN		Date of death
Diagnosis	Length of EN	**Severity of illness**	Time to death from start of feed
	Need for combination feeding		Cause of death
	Method of feed administration	APACHE II score	
Operative Data	Volume of feed prescribed	SIRS / Sepsis syndrome	
	Volume of feed administered	ASA	
Surgery during admission	Cumulative energy balance		
Operation performed	Weekly energy surplus/deficit		
Date of operation	Time to achieve tolerance		
	Episodes of intolerance		

Table 5.1: Main variables recorded.

measurements also permitted nutritional requirements to be calculated by senior dieticians according to the Schofield method (Todorovic and Micklewright, 2004; appendix 4). These calculations aimed at providing target intakes of 20 – 25 kcal kg^{-1} d^{-1} non-protein energy and approximately 0.17g nitrogen kg^{-1} d^{-1}. This load was administered along the unit's practices of optimal nutritional support (Woodcock and MacFie, 2002; Chahal *et al*., 2004; Woodcock and MacFie, 2004) and as guided by strict nutrition team feeding protocols.

Briefly, feeding was administered orally or enterally whenever possible, with deficiencies in oral intake being supplemented with enteral feed administration till the nutritional requirements were met. If patients did not tolerate adequate intake via the oral and/or enteral routes, parenteral supplementation was instituted to make up the difference in nutritional requirements. Patients were only placed on 'total' PN when their clinical condition dictated that their gut could not be used for feeding or when previous attempts at establishing oral or enteral feeding had failed. Patients would move up or down this continuum of nutrition depending primarily on tolerance of feeding by the gut. At any one time an individual patient could be receiving up to three modalities of feeding by the way of oral, enteral and/or parenteral intake, with the proportion of each changing regularly depending on enteral tolerance. This method of feeding ensured high success rates of achieving nutritional targets as previously validated in our unit (Chahal *et al*., 2004). This required significant clinical input, with patients being assessed regularly by the author or other members of the hospital's multidisciplinary nutrition team, which also permitted the accurate documentation of other data points.

Clinicians were free to use whichever method of parenteral or EN they deemed appropriate. As such clinicians could use NG, NJ, PEG, percutaneous endoscopic gastrojejunostomy (PEGJ) or percutaneous endoscopic jejunostomy (PEJ) enteral feeding as was their usual practice. Similarly, for those patients receiving intravenous nutrition, this was administered via a peripheral route, a peripherally inserted central cannula (PICC) or through a central or tunnelled (Hickman) line as deemed clinically appropriate by the attending physician. Different methods of feed administration were recorded. Feeds were standardized and were administered in a volume sufficient to meet daily nutritional requirements. Commercially available preparations were used as follows: EN was provided using Fresubin Original® 1 kcal ml^{-1} polymeric feed (Fresenius Kabi Ltd, Cheshire, United Kingdom), peripheral PN was administered using Kabiven® peripheral 9 (Fresenius Kabi Ltd, Cheshire, United Kingdom), a 0.7 kcal ml^{-1} peripheral parenteral feed, while Kabiven® 14 (Fresenius Kabi Ltd, Cheshire, United Kingdom), a 0.9 kcal ml^{-1} parenteral feed for central venous administration, was used for central TPN administration. The availability of these feeds was determined solely by hospital contracts active at the time and as such there were no commercial (or other) biases on the part of the author in their use. Constituents of these feeds are summarised in appendix 5.

Tolerance to oral or enteral feeding was recorded hourly for the duration of hospital stay. Fluid balance charts, food charts and diet diaries, together with regular clinical reviews were used to collate this data. Episodes of intolerance were determined by documented episodes of vomiting, feed aspiration, severe abdominal pain, distension or bloating that necessitated cessation or alterations to feed administration. Patients were considered to

have achieved enteral tolerance when they were able to retain ≥80% of their calculated nutritional requirements by the oral / enteral routes for a minimum contiuous period of ≥48 hours. The time necessary for a patient to achieve enteral tolerance from the instigation of feeding was documented in hours. Non-protein energy administration was determined and compared to calculated nutritional requirements to permit cumulative energy balances as well as weekly energy surplus/deficit assessments to be ascertained. The length of adjuvant feeding was documented and the appropriateness of nutritional support was assessed by a minimum of five days of feed administration.

Evidence of single organ failures was determined along standard clinical and biochemical lines together with criteria used in the APACHE II, Glasgow Coma Scale (GCS), and the SOFA score (appendix 3). Cardiac, respiratory, renal, hepatic, haematological, and neurological failure were ascertained in this way. Adequate gut function was determined by the oral or enteral tolerance of ≥80% of calculated nutritional requirements for a minimum contiuous period of ≥48 hours. Anything less than this was considered to represent a state of gut failure.

In view of the heterogeneity of patients included in this study, disease severity was assessed using the APACHE II scoring system according to parameters measured at the time of commencement of feeding (appendix 3). All complications during hospital stay were documented prospectively and grouped into feed related, delivery related or septic complications. For purposes of this study, septic morbidity was defined as the presence of recognized pathogens in body tissues that are normally sterile, confirmed by the results of

culture and supported by clinical, radiological, or haematological evidence of infection as follows:

- A chest infection was recorded with the isolation of pathogens in purulent sputum, with or without evidence of consolidation or pneumonia on chest x-ray.

- A wound infection was recorded with the isolation of pathogens in pus or discharge from a wound.

- A urinary tract infection was recorded when there was evidence of a bacteruria at a concentration of 10^5 organisms/ml urine together with other signs of infection in case of a catheter specimen.

- A percutaneous endoscopic gastrostomy (PEG) or jejunostomy site infection was recorded with the isolation of pathogens from an inflamed exit site. Similarly, a line infection was recorded with the isolation of pathogens from line tips or discharge from an inflamed exit site.

- An intra-abdominal abscess was recorded with the isolation of pathogens from an intra-abdominal collection requiring percutaneous or open drainage.

- Septicaemia was recorded with the isolation of pathogens in peripheral venous blood in the absence of an overt focus of infection.

A patient was designated as manifesting SIRS if they demonstrated two or more of the following criteria: a temperature of >38^{o}C or <36^{o}C, a heart rate of >90 beats per minute, a respiratory rate of >20 per minute or a $PaCO_2$ <32 mm Hg, and a white cell count (WCC) of >12 or <4 x 10^9 L^{-1} (Bone, Balk and Cerra, 1992).

5.2.1 Statistical analysis

Results were tabulated on an Excel® spreadsheet (Excel for Windows®, Microsoft Corporation, Redmond, Washington, USA) and then analysed using SPSS® for Windows® version 11.5 (SPSS®, Chicago, Illinois, USA). All parametric data were expressed as means (SD) and nonparametric data as medians (IQR). Comparisons between groups were made using Student's *t*-test or Mann-Whitney *U* test for quantitative data as appropriate. Qualitative data was assessed using the χ^2 test or corresponding Fisher's exact test for small cohorts. A p-value of less than 0.05 was taken to signify a statistically significant difference.

Factors associated with outcome at 6 months were identified using univariate analysis and these were then evaluated for independent prognostic significance using a logistic regression analysis model. Odds ratios (OR) and 95 per cent confidence intervals (C.I.) for these variables were quoted. Assumptions for multivariate analysis were assessed (Pallant, 2002). Possible associations between variables were further investigated by manipulating the resulting model and by sequentially eliminating variables from the

analysis.

Data relating to death from the instigation of feeding was presented diagrammatically by plotting Kaplan-Meier plots showing survival curves for patients with adequate gut function separate from those with gut failure. The importance of the state of gut function, as defined by enteral tolerance, on prognosis was assessed for sensitivity, specificity, PPV, NPV, the number needed to diagnose (NND; calculated as $^{1}/_{[\text{sensitivity} -(1\text{-specificity})]}$) and the number needed to treat (NNT; calculated as $^{1}/_{\text{difference in proportions}}$). 95 per cent confidence intervals (C.I.) for these variables were also presented.

The data was also analysed in such a way as to assess those factors which were independently associated with gut failure. Factors associated with gut failure were similarly identified using univariate analysis and these were then evaluated for independent association using a multivariate logistic regression model for this dichotomous variable. Assumptions for this multivariate analysis were checked in a similar fashion to the methodology described above.

A sample size calculation for generalisability was based on the method for standard (as opposed to stepwise) regressions analysis described by Tabachnick and Fidell (1996) using the formula $N > 50 + 8m$ (where N is the minimum size of the whole cohort and m is the number of independent variables). Assuming 10 independent variables associated with outcome at 6 months, a minimum total sample size of 130 patients would be required for purposes of generalizability.

5.3 RESULTS OF THE VALIDATION PROCESS

A total of 315 patients (M:F = 181:134, mean age 64.2 (±17.6) years) were recruited during the 21 month study period, of which 101 (32%) died during the first six-months of follow-up. Demographic data and other characteristics for these patients are summarised in Table 5.2. Fifty (16%) patients demonstrated evidence of gut failure, of which 44 (88%) died, when compared to a mortality of around 22% in patients with an adequately functioning gastrointestinal tract as defined by the oral/enteral tolerance of $\geq$80% of calculated nutritional requirements for 48 hours or more ($p<0.001$).

To assess for factors which were associated with outcome at 6 months, comparisons were made between the 214 patients who were alive at the end of this follow-up period and the 101 patients who died during this time interval. These are summarised in Table 5.2. On univariate analysis, increased age ($p<0.001$), lower nutritional requirements ($p<0.001$), curtailed feeding for less than 5 days ($p=0.002$), the presence of complications ($p=0.006$), and the development of septic complications ($p<0.001$) were all negative prognostic indicators. In addition, the presence of cardiac ($p<0.001$), respiratory ($p<0.001$), renal ($p<0.001$), neurological ($p<0.001$), hepatic ($p=0.017$), and gut failure ($p<0.001$), together with higher APACHE II scores ($p<0.001$) were also associated with poorer outcomes. These variables were analysed using multivariate logistic regression to assess for independent association with outcome at 180 days. For purposes of co-linearity, the presence of complications was excluded from the statistical model in favour of the presence of septic complications. APACHE II scores were also excluded for similar

Factor	Whole cohort	Alive at 6 months	Dead at 6 months	P-value
Patients	315	214	101	–
Demographics				
Age (years) *	64.2 (±17.6)	59.7 (±18.5)	73.6 (±10.4)	**<0.001**
Sex				0.324 ‡
Male	181 (57.5%)	127 (59.3%)	53. (53.5%)	
Female	134 (42.5%)	87 (40.7%)	47 (46.5%)	
Hospital Stay				
Admitted to ICU	183 (58.1%)	117 (54.7%)	66 (65.3%)	0.073
Needed surgery	160 (50.8%)	116 (54.2%)	44 (43.5%)	0.148
Length of hospital stay (days) *	23 (15–39)	23 (15–42)	23 (13–33)	0.187
Nutritional parameters				
Height (meters)	1.70 (1.61–1.76)	1.70 (1.61–1.76)	1.70 (1.61–1.72)	0.573
Weight (kg)	70.0 (59.1–81.0)	72.0 (56.8–82.0)	68.5 (60.1–79.4)	0.580
BMI *	24.8 (20.6–29.0)	24.8 (20.0–30.1)	24.5 (21.5–27.8)	0.982
Nutritional requirements (kcal/day) *	1577 (±288)	1624 (±306)	1476 (±215)	**<0.001**
Length of feeding (days) *	7 (5–14)	8 (5–15)	7 (4–14)	0.069
<5 days of feeding	70 (22.2%)	37 (17.3%)	33 (32.7%)	**0.002**

Factor	Whole cohort	Alive at 6 months	Dead at 6 months	P-value
Organ Failure				–
Cardiac Failure	78 (24.8%)	36 (16.8%)	42 (41.6%)	**<0.001**
Respiratory failure	104 (33.0%)	50 (23.4%)	54 (53.5%)	**<0.001**
Renal failure	44 (14.0%)	11 (5.1%)	33 (32.7%)	**<0.001**
Hepatic failure	15 (4.8%)	6 (2.8%)	9 (8.9%)	**0.017**
Neurological failure	24 (7.6%)	9 (4.2%)	15 (14.9%)	**<0.001**
Haematological failure	5 (1.6%)	1 (0.5%)	4 (4.0%)	0.076 ‡
Gut failure	50 (15.9%)	6 (2.8%)	44 (43.6%)	**<0.001**
Complications				
Any	158 (50.1%)	94 (43.9%)	64 (63.3%)	**0.006**
Septic	98 (31.1%)	45 (21.0%)	53 (52.5%)	**<0.001**
Feed related	86 (27.3%)	50 (23.3%)	36 (35.6%)	0.059
Delivery system related	86 (27.3%)	61 (28.5%)	25 (24.8%)	0.240
APACHE II score *	12 (8–15)	10 (7–14)	15 (11–20)	**<0.001**
Mortality				
Death by 180 days	101 (32.1%)	-	101 (100%)	-
Time to death (days) *	15 (7–31)	-	15 (7–31)	-

Table 5.2: Factors associated with outcome at 6 months on univariate analysis. Factors which are associated with outcome at 6 months are highlighted. (* results denote median (IQR); ‡ Fischer' s exact test)

reasons of co-linearity.

Results of the logistic regression analysis are shown in Table 5.3. From these results, it is apparent that an increase in age ($p<0.001$; OR 1.068; 95%CI 1.036, 1.101), the development of septic complications ($p=0.001$; OR 3.093; 95%CI 1.543, 6.202), and the presence of renal ($p<0.001$; OR 5.903; 95%CI 2.077, 16.780), neurological ($p=0.048$; OR 3.566; 95%CI 1.009, 12.607) and gut failure ($p<0.001$; OR 16.121; 95%CI 5.374, 48.354), were all independently associated with outcome. Individuals who passed away in the first 6 months of follow-up were 16 times more likely to have manifested gut failure than patients who survived (Table 5.3). Manipulation of the model was performed by sequential elimination of cardiac and then respiratory failure from the analysis to assess whether possible interdependence of these variables could have resulted in their loss of association with outcome on multivariate analysis. The exclusion of one or the other factor from the model had no effect on their respective association with outcome (results of model manipulation are not shown).

In a similar fashion, comparisons were made between the 265 patients who manifested adequate gut function and the 50 patients who had inadequate function to assess for factors which were associated with gut failure. These are shown in Table 5.4. On univariate analysis, increased age ($p<0.001$), lower nutritional requirements ($p<0.001$), curtailed feeding ($p<0.001$), the presence of complications ($p=0.006$), and the development of septic complications ($p=0.001$) were all associated with gut failure. In addition, the presence of cardiac ($p=0.006$), respiratory ($p=0.014$), renal ($p<0.001$),

Factor	P-value	Odds ratio (95% C.I.)
Demographics		
Age	**<0.001**	**1.068 (1.036, 1.101)**
Nutritional parameters		
Nutritional requirements (kcal/day) *	0.092	0.999 (0.998, 1.000)
<5 days of feeding	0.617	1.249 (0.523, 2.979)
Complications		
Septic	**0.001**	**3.093 (1.543, 6.202)**
Organ Failure		
Cardiac Failure	0.914	0.941 (0.312, 2.839)
Respiratory failure	0.198	2.004 (0.695, 5.782)
Renal failure	**0.001**	**5.903 (2.077, 16.780)**
Hepatic failure	0.413	1.750 (0.458, 6.681)
Neurological failure	**0.048**	**3.566 (1.009, 12.607)**
Gut failure	**<0.001**	**16.121 (5.374, 48.354)**

Table 5.3: Results of the multivariate logistic regression analysis performed with factors associated with outcome on univariate analysis. Factors which are independently associated with outcome at 6 months are highlighted.

Factor	Whole cohort	Adequate gut function	Inadequate gut function	P-value
Patients	315	265	50	–
Demographics				
Age (years) *	64.1 (±17.6)	62.2 (±17.9)	74.6 (±11.2)	**<0.001**
Sex				0.589
Male	181 (57.5%)	154 (58.1%)	27 (54.0%)	
Female	134 (42.5%)	111 (41.9%)	23 (46.0%)	
Hospital Stay				
Admitted to ICU	183 (58.1%)	151 (57.0%)	32 (64.0%)	0.356
Needed surgery	160 (50.8%)	137 (51.7%)	23 (46.0%)	0.543
Length of hospital stay (days) *	23 (15–39)	26 (15–41)	15 (9–30)	**<0.001**
Nutritional parameters				
Height (meters)	1.70 (1.61–1.76)	1.70 (1.61–1.76)	1.70 (1.61–1.72)	0.511
Weight (kg)	70.0 (59.1–81.0)	70.8 (58.7–81.7)	69.9 (60.0–75.9)	0.515
BMI *	24.8 (20.6–29.0)	24.9 (20.6–29.3)	24.3 (20.8–26.9)	0.737
Nutritional requirements (kcal/day) *	1577 (±288)	1597 (±291)	1471 (±252)	**0.002**
Length of feeding (days) *	7 (5–14)	8 (5–16)	4 (2–8)	**<0.001**
<5 days of feeding	70 (22.2%)	42 (15.8%)	28 (56.0%)	**<0.001**
Time to tolerance (hours) *	-	141 (71–216)	-	-

Factor	Whole cohort	Adequate gut function	Inadequate gut function	P-value
Organ Failure				–
Cardiac Failure	78 (24.8%)	58 (21.9%)	20 (40.0%)	**0.006**
Respiratory failure	104 (33.0%)	80 (30.2%)	24 (48.0%)	**0.014**
Renal failure	44 (14.0%)	29 (10.9%)	15 (30.0%)	**<0.001**
Hepatic failure	15 (4.8%)	9 (3.4%)	6 (12.0%)	**0.009**
Neurological failure	24 (7.6%)	14 (5.3%)	10 (20.0%)	**<0.001**
Haematological failure	5 (1.6%)	3 (1.1%)	2 (4.0%)	0.360 ‡
Complications				
Any	158 (50.1%)	123 (46.4%)	35 (70.0%)	**0.006**
Septic	98 (31.1%)	73 (27.5%)	25 (50.0%)	**0.001**
Feed related	86 (27.3%)	69 (26.0%)	17 (34.0%)	0.401
Delivery system related	86 (27.3%)	70 (26.4%)	16 (32.0%)	0.625
APACHE II score *	12 (8–15)	11 (7–14)	17 (12–22)	**<0.001**
Mortality				
Death by 180 days	101 (32.1%)	57 (21.5%)	44 (88.0%)	**<0.001**
Time to death (days)	21 (8–58)	31 (15–100)	7 (4–16)	**<0.001**

Table 5.4: Factors associated with gut failure on univariate analysis. Factors which are associated with gut failure are highlighted. (* results denote median (IQR); ‡ Fisher's exact test)

neurological ($p<0.001$), and hepatic ($p=0.009$) failure, together with higher APACHE II scores ($p<0.001$) and shorter hospital stays ($p<0.001$) were also similarly associated with IGF. These variables were analysed using multivariate logistic regression to assess for independent association with outcome at 180 days. For purposes of co-linearity, the presence of complications was excluded from the statistical model in favour of the presence of septic complications. Similarly, the continuous variable of length of feeding was excluded in favour of the categorical variable <5 days of feeding. APACHE II scores, length of hospital stay and time to death were also considered as dependent variables and were therefore excluded from the model.

Results of the logistic regression analysis are shown in Table 5.5. From these results, it is apparent that an increase in age ($p<0.027$; OR 1.068; 95%CI 1.005, 1.090), curtailed feeding of less than 5 days ($p<0.001$; OR 10.137; 95%CI 3.975, 25.852) and mortality by 180 days ($p<0.001$; OR 16.081; 95%CI 5.356, 48.282), were all independently associated with gut failure. IGF was not independently associated with the development of septic complications ($p=0.255$; OR 1.688; 95%CI 0.685, 4.158).

Manipulation of the model was once again performed by sequential elimination of cardiac and then respiratory failure from the analysis to assess whether possible interdependence of these variables could have resulted in their loss of association with outcome on multivariate analysis. The exclusion of one or the other factor from the model had no effect on their respective association with outcome (results not shown). Similarly, less than 5 days of feeding was also excluded because of possible co-linearity

Factor	P-value	Odds ratio (95% C.I.)
Demographics		
Age	**0.027**	**1.068 (1.005, 1.090)**
Nutritional parameters		
Nutritional requirements (kcal/day)	0.418	0.999 (0.997, 1.001)
<5 days of feeding	**<0.001**	**10.137 (3.975, 25.852)**
Complications		
Septic	0.255	1.688 (0.685, 4.158)
Organ Failure		
Cardiac Failure	0.077	3.723 (0.866, 15.996)
Respiratory failure	0.143	0.339 (0.080, 1.440)
Renal failure	0.935	0.953 (0.296, 3.069)
Hepatic failure	0.062	4.141 (0.930, 18.442)
Neurological failure	0.131	2.625 (0.751, 9.177)
Mortality		
Death by 180 days	**<0.001**	**16.081 (5.356, 48.282)**

Table 5.5: Results of the multivariate logistic regression analysis performed with factors associated with the state of gut failure on univariate analysis. Factors which are independently associated with gut failure are highlighted.

with mortality data, but once again little change to the results was noted (results of model manipulation are not shown).

Further analysis demonstrated that patients with IGF were 16 times more likely to die by 6 months when compared to those with a functioning gastrointestinal tract (Table 5.5). This difference in mortality between the two groups is shown graphically in the Kaplan Meier survival plot in Figure 5.1. From this plot, it is evident that the majority of deaths in both groups occurred during the first month of follow-up. The sensitivity, specificity, PPV, NPV, NND and NNT on outcome at 6 summarised in Table 5.6.

5.4 DISCUSSION OF THE VALIDATION PROCESS

The results of this study demonstrate that in this cohort of 315 patients, the state of gut function, as quantifiably defined by enteral tolerance, is an independent indicator of prognosis. Most patients with gut failure die early, often within the first 30 days of follow-up. The cause of death in these patients is unclear but was not independently associated with the detection of septic complications. In addition, results from this study suggest that the effective and timely treatment of patients with gut failure can potentially save numerous lives. The fact that the gut is involved in many vital homeostatic mechanisms makes observations from this study about the importance of gut failure on prognosis all the more plausible.

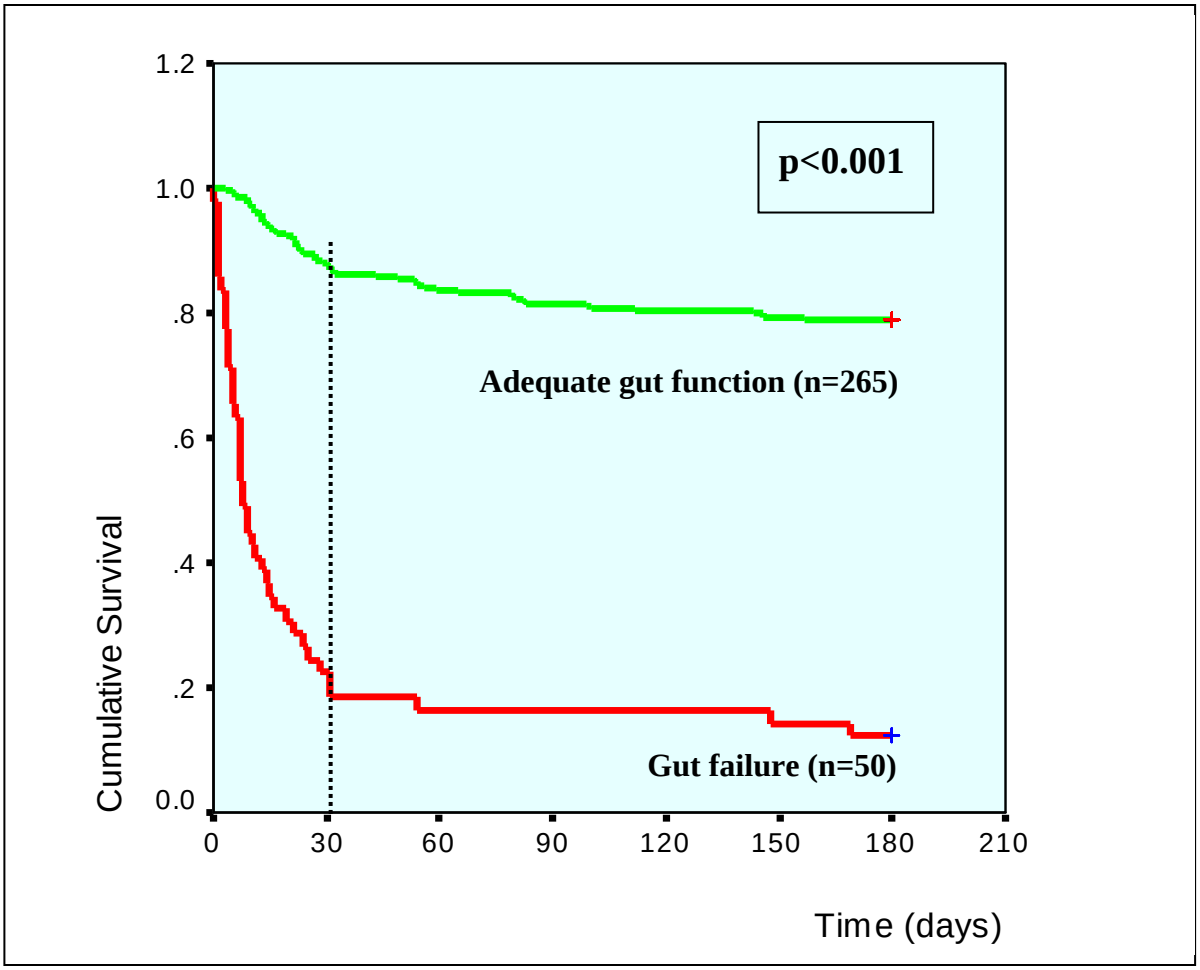


Figure 5.1: Kaplan-Meier survival plot for the first 180 days of follow-up for patients with and without gut failure (shown respectively in red and green). The difference in survival between the two groups was statistically significant ($p<0.001$). The majority of deaths in both groups occurred in the first 30 days (dotted line).

Variable	Tolerance of ≥80% for ≥48 hours
Patients (%)	265 (84.1%)
Sensitivity (95% C.I.)	0.972 (0.947, 0.987)
Specificity (95% C.I.)	0.436 (0.383, 0.467)
PPV (95% C.I.)	0.785 (0.765, 0.797)
NPV (95% C.I.)	0.880 (0.773, 0.943)
NND (95% C.I.)	2.453 (2.207, 3.031)
NNT (95% C.I.)	1.504 (1.353, 1.858)
P-value	<0.001

Table 5.6: Association between survival and the tolerance by the gut of ≥80% of nutritional requirements for 48 hours or more.

This study was rigorous with the methodology employed. All data points were meticulously defined prior to the commencement of the study to allow for consistent data collection. The data was also cross referenced with available medical, dietetic and patient administration records prior to analysis to ensure concordance. In addition, numerous factors that were known or have been reported to be associated with outcome were assessed simultaneously in an attempt to decrease the potential bias associated with studying only those variables of direct interest to this work. The author recognises that this methodology has its limitations. A considerable amount of data needed to be collected for each individual patient, making the study extremely laborious to undertake. Standardization of the data collection went some way in facilitating this. The large number of variables also meant that some factors may have achieved significance solely on the basis of chance. However, the author is of the opinion that the staggered univariate to multivariate approach of data analysis chosen for this study should have decreased the opportunity for this error in data analysis.

A definition of adequacy of gut function based on the tolerance of calculated nutritional requirements may be perceived to disadvantage those patients with higher nutritional requirements. On a purely theoretical basis, the higher one's requirements, the more feed the gut has to accept to achieve tolerance, and therefore the greater the chance of failure. Results from this study suggest the opposite. Patients with higher nutritional requirements were more likely to have adequate gut function despite the fact that they had to tolerate more feed. In turn they had a better outcome overall. Patients who died at 6 months had lower overall nutritional requirements when compared to survivors. This is

in agreement with the literature that suggests that well nourished or obese patients with higher nutritional requirements are more likely to have a better outcome than cachectic or malnourished patients with lower requirements (Garrouste-Orgeas *et al*., 2004; Aldawood, Arabi and Dabbagh, 2006; Peak *et al*., 2006; Zamora *et al*., 2007). A definition of gut function based on enteral tolerance does not bias in favour of patients with lower nutritional requirements.

The fact that on multivariate analysis there was no association between gut failure and sepsis may appear to be at variance with the gut origin of sepsis hypothesis. There are at least three possible explanations for this result. Firstly this may represent a type II statistical error because the number of patients that manifested gut failure in this study was relatively small; however it is the author's opinion that this is unlikely. Alternatively, it may be possible that gut failure causes overwhelming sepsis and death before sepsis becomes clinically apparent or detectible. This may help to explain the pathogenesis of some cases which are labelled as exhibiting 'pyrexia of unknown origin'. Finally, it is plausible that gut failure results in death by means other than sepsis, such as by means of SIRS and an uncoordinated cytokine response, with the development of infection representing little more than an epiphenomenon in an otherwise immunocompromised host. The results of Deitch and co-workers (Deitch, 2001; Deitch, 2002; Deitch *et al*. 2006) supports this contention. These investigators have proposed that BT and resultant sepsis is not essential for the cascade of events eventually resulting in MOF. In their theoretical model, called the multi-hit hypothesis (Figure 1.3), the deleterious effects leading to MOF are brought about by a deregulated cytokine cascade. This cytokine

imbalance which ultimately overcomes the host result in, but does not necessarily require, BT for its propagation. This corroborates work published by Moore and co-workers who failed to demonstrate bacteria or endotoxins in portal venous blood of polytrauma patients (Moore *et al*., 1991; Koike *et al*, 1994). The gut, as the body's single largest immunological and cytokine producing organ is hypothesised to play a central role in perpetuating this process, but the exact mechanisms concerned remain unclear.

Further elucidation of the homeostatic upset caused by gut failure and the pathways involved in the development of MOF and delayed death may be important in developing effective strategies to treat this deleterious cascade of events. From this study, survival analysis demonstrates that almost all patients with gut failure died. Most succumbed in the first month, with the median (IQR) time to death being 7 (4–16) days. Contrary to popular belief, this observation makes it unlikely for malnutrition to be a major contributor to death in patients with gut failure. Further, optimal nutrition practices in the index institution would have meant that these patients would have been receiving TPN to prevent this eventuality. Sepsis, on the other hand, was not independently associated with gut failure, as mentioned above. This early death with gut failure appears to be the result of a catastrophic event, one which currently eludes detection in daily clinical practice. It is increasingly plausible that this event is a result of a rapid and profound imbalance between anti-inflammatory and pro-inflammatory cytokines, rapidly spiralling out of control, resulting in SIRS, MOF and eventually death. Trials which study specific cytokine levels and cytokine ratios are necessary to investigate this hypothesis.

Another finding from this study was that cardiac and respiratory failure, both traditional prognostic indicators, failed to show independent association with outcome at six months, while other organ insufficiencies, including neurological and gut failure, were associated with outcome independently of other prognostic factors. Data from this study do not provide adequate explanations for this observation. The author speculates that this may relate to the fact that cardiac and respiratory function are intensely monitored in daily clinical practice, and aggressively treated with a battery of effective therapies and interventions when they fail. The same cannot be said for gut failure, for which there are, to date, no effective therapies. It is plausible that it is not failure of the organs *per se* which is a prognostic indicator; rather, inadequately treated or irreversible organ failures condition outcome. The inference from this is that early detection and effective and aggressive treatment of gut failure holds a potential to save numerous lives. The independent association of gut failure with increased mortality may justify the development of gut-directed therapies aimed at preventing gastrointestinal failure or attenuating the period of established gut dysfunction.

5.5 CONCLUSION: A VALIDATED DEFINITION OF GUT FAILURE

In conclusion, adequacy of gut function may be defined by the tolerance of a quantifiable oral or enteral challenge. More specifically, the tolerance of 80% or more of calculated nutritional requirements for a continuous period of at least 48 hours may be used to identify those patients in whom the gut is working adequately from those in whom it is

not. This test to establish gut failure or function is easily applicable clinically.

Characterised in this way, gut failure becomes an independent indicator of clinical outcome. It remains to be seen whether therapies can be developed to accelerate the return of normal gut function and attenuate periods of gut failure. These therapies could, in theory, be associated with real improvements to patient outcomes but further research is necessary.

CHAPTER 6:

PREPYLORIC & POSTPYLORIC FEEDING: THE SIGNIFICANCE OF THE SITE OF FEED DELIVERY TO ENTERAL TOLERANCE.

'The difficulty lies not in the new ideas,
but in escaping the old ones.'

John Maynard Keynes
(1883 –1946)

6.1 INTRODUCTION

Defining gastrointestinal performance in terms of enteral tolerance is challenging. The main difficulty lies in the fact that a number of extraneous factors, in particular the site of enteral feed administration, have been suggested to affect tolerance, and therefore, by inference, the state of gut function. It is said that postpyloric feeding, by delivering nutrients further down the gastrointestinal tract and bypassing the stomach, facilitates the tolerance of enteral feeding, and increases the number of patients who achieve this end point (Heyland *et al*., 2004). If this were to be the case, then any definition of gut function based on enteral tolerance would have to take into account, and possibly correct for, the site of feed administration.

Definite conclusions about the importance of the site of feed delivery on patients' ability to achieve enteral tolerance cannot be reliably drawn from the literature. Published studies comparing pre and postpyloric feeding are biased in favour of the latter, partly because of a failure to factor for the main disadvantage of postpyloric feeding, namely the difficulty and time necessary to place tubes beyond the pylorus. This chapter aims to address this issue.

Two studies are described sequentially. The first describes and validates a bedside technique of postpyloric tube placement, necessary groundwork for the second study aimed at comparing pre *versus* postpyloric feeding and the effects of changing feed delivery site on the proportion of patients achieving enteral tolerance. For purposes of

convenience, enteral tolerance was similarly defined as the tolerance of 80% or more of calculated nutritional requirements over a minimum continuous period of 48 hours.

6.2 DEVELOPING AND VALIDATING A BEDSIDE TECHNIQUE OF POSTPYLORIC TUBE PLACEMENT: INTRODUCTION

The administration of enteral feeds beyond the pylorus has been suggested as a method to improve feed tolerance and offers an alternative route of feed administration when prepyloric EN fails. However, the placement of postpyloric feeding tubes is fraught with difficulties both to organize and subsequently to establish feeding tube insertion. Historically, postpyloric feeding tubes have been inserted using endoscopy or fluoroscopy with varying success (Shipps *et al.*, 1979; Rives *et al.*, 1989). These techniques have the advantage of inserting feeding tubes under visual guidance with rates of success in excess of 75 per cent in many studies (Hillard *et al*., 1995; Hernandez-Socorro *et al*., 1996). However, tube placement by radiology or endoscopy also present a number of drawbacks, including the increased time required for initiation of feeding, the occasional need to transfer patients to endoscopy or radiology suites, the inherent risks associated with these procedures, and the need for specialized staff to ensure correct insertion. These problems are further compounded if and when tubes get blocked or dislodged necessitating repositioning. It has been suggested that these drawbacks may outweigh any potential benefits of postpyloric feeding and provide a justification for the development of techniques of tube insertion that can be used by the bedside, are safe and

provide cost-effective routes of nutritional support.

This study describes an observational study of one such a method of postpyloric tube placement. The primary aim of this trial was to validate the success of this technique. A secondary aim was to assess the time to establish EN using bedside NJ tube placement. In addition, the value of aspirate pH as an indicator of tube tip placement was evaluated, as was the discomfort of feeding tube insertion experienced by patients.

6.3 METHODS

Consecutive patients in one institution requiring enteral nutritional support were observed. A single researcher was informed of all patients considered for EN by the attending physician or dietician. Subject to consent for tube insertion and the inclusion criteria summarised in Table 6.1, all patients underwent NJ intubation. A total of 43 NJ tubes were inserted in 32 patients. X-ray confirmation of the tube tip position was obtained prior to the commencement of feeds. Patients were then followed up till the discontinuation of feeding and data was collected prospectively.

Inclusion criteria	Exclusion criteria
- All patients needing enteral feeding	- Candidates for PEG / PEGJ - Contraindication to metoclopramide - Age <18 years - Pregnancy - Intolerance to intubation

Table 6.1: Inclusion and exclusion criteria.

(PEG, percutaneous endoscopic gastrostomy;

PEGJ, percutaneous endoscopic gastrojejunostomy)

6.3.1 End points and statistical analysis

The primary outcome was the position of the tube tip after attempted intubation. Portable chest and abdominal x-rays were taken in all patients after tube insertion to confirm tube tip position. In the case of failed postpyloric placement, no further attempts were made to achieve the required position if the tube was proven radiologically to be placed in the stomach. X-rays were repeated weekly during the duration of feeding and where possible immediately prior to tube removal to assess for tube tip displacement.

The main secondary outcome measures were the time necessary to insert the tubes and the time necessary to establish EN from the clinicians' decision to feed the patient. This latter time period was calculated from the time the investigator was informed of the intention to feed the patient to the time the feed actually started. A subsidiary aim was to assess the pH of any aspirate obtained during tube insertion, and whether this could be reliably used as an indicator of tube tip position. The pH of aspirate obtained at time of tube insertion was assessed with Multistix® 10 SG (Bayer Diagnostics Mfg., Ltd. Bridgend, UK) reagent strips as well as by using an electronic handheld pH meter (Hanna pH tester, Progen Scientific Ltd, Mexborough, UK) which was regularly calibrated as recommended by the manufacturer and which gave digital pH readings between the pH of 0 and 14 to the closest two decimal points. A pH of $\leq$5 was considered to indicate gastric passage (Phang *et al*., 2004). The administration of any acid suppressing medications in the 2 weeks prior to tube insertion was also recorded.

The patients' perspective of nasoenteral tube discomfort was assessed immediately after tube insertion and at 24 hours from tube placement. One hundred millimetre visual analogue scores without intersections were employed for this purpose.

Non-weighted Corflo®, Merck; 140cm long Fr 8 feeding tubes (Merck Pharmaceuticals, Windsor, Berkshire, UK) were used throughout the study. Tubes were selected based on a number of characteristics necessary to the study design. They were both easily and widely available, had graduations at every 5cm, showed good radiological visibility, and an indwelling guide wire. The tubes were available in the index institution and as such the author had no financial interest or other biases in selecting to use these tubes.

Results were tabulated on an Excel® spreadsheet (Excel for Windows®, Microsoft Corporation, Redmond, Washington, USA) and then analysed using SPSS® for Windows® version 11.5 (SPSS®, Chicago, Illinois, USA). Results obtained were expressed as medians (IQR). Dependent variables were assessed using the Wilcoxon sign rank test. Statistical significance was considered at the 5 per cent level.

6.3.2 Technique of bedside nasojejunal tube placement (Figure 6.1):

This intubation technique involved three distinct stages; those of oesophageal, gastric and postpyloric placement. Key to the success of this technique was the confirmation of tube tip position at each phase and prior to proceeding to the next stage.

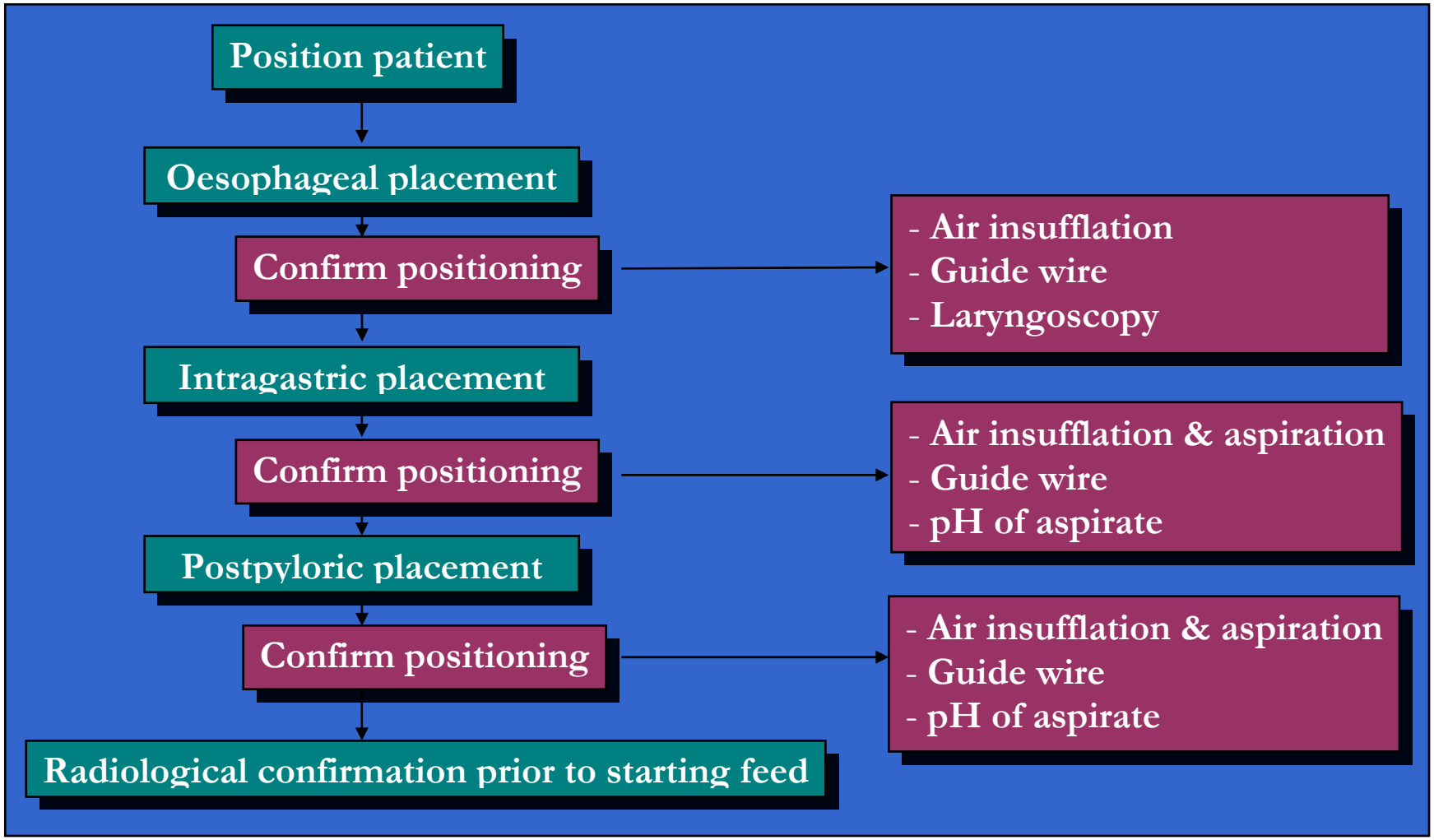


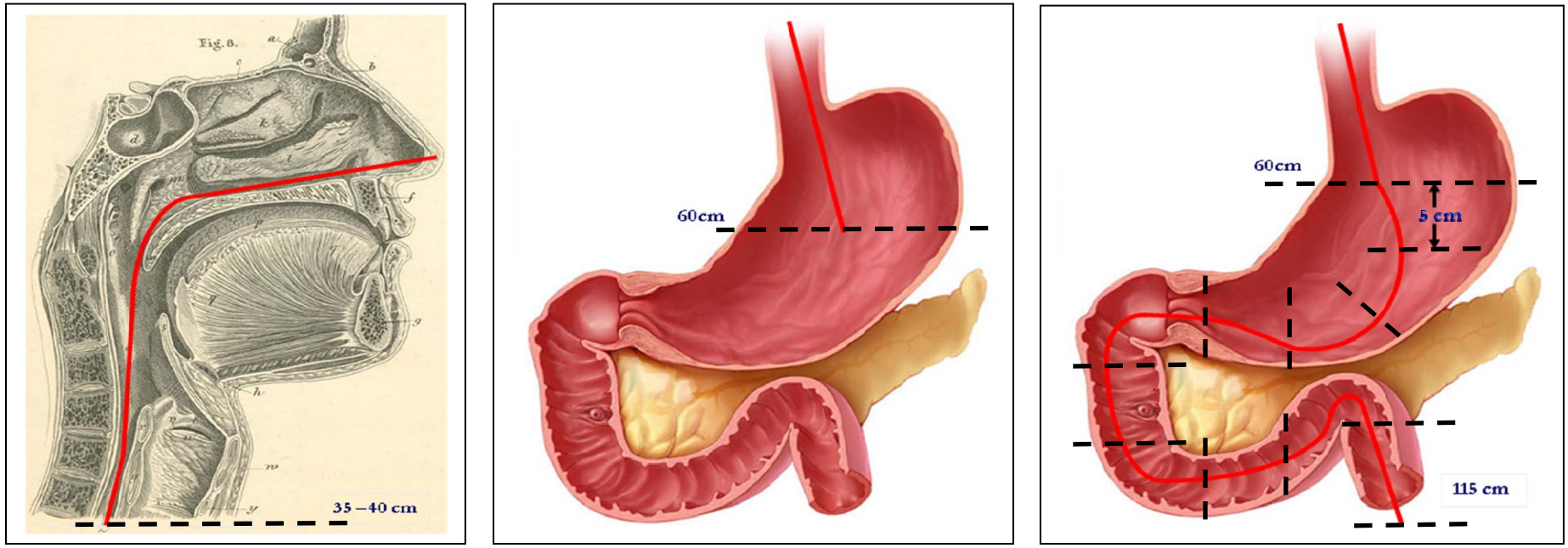
Figure 6.1: Flow diagram summarising the method of NJ tube insertion.

Preparation & positioning: Patients were administered 10mg metoclopramide intravenously 15 to 30 minutes prior to tube insertion. Having prepared the necessary equipment (Table 6.2), the tube was checked for integrity and the internal lumen was then lubricated by flushing with 10ml of sterile water. The indwelling guide wire was partially withdrawn and all the water from within the lumen was emptied to avoid aspiration. The guide wire was then repositioned and the patient was placed supine with the head of the bed raised at 30 to 45 degrees. The tube was looped behind the patient's ear and the distance from the tip of the ipsilateral nostril to the xiphisternum was measured as an estimate of the depth of insertion necessary for the tube tip to lie within the stomach. The feeding tube was then externally lubricated with aqueous gel.

Oesophageal placement (Figure 6.2a): Cooperative patients with an intact gag reflex were asked to take a sip of water and keep this in the mouth. The tube was then passed into the nostril, parallel to the hard palate. As soon as the tube was felt to touch the back of the nasopharynx, the patient was asked to swallow while the tube was simultaneously advanced to 35 to 40cm. At this level, oesophageal placement was confirmed by a combination of air insufflation with auscultation in the epigastrium (the 'whoosh test'; Dawson, 2007), and by assessing for coiling using the indwelling guide wire. If doubt still existed as to oesophageal placement, laryngoscopy was performed in unconscious patients to exclude the possibility of tracheo-bronchial intubation. Finally, if placement in the oesophagus could not be confirmed, the tube was withdrawn back into the nose, and further attempts at oesophageal placement were made.

- Fine-bore feeding tube
- 2x 10ml syringes
- 2x 20ml syringes
- 20ml water for injection
- Lubricating gel
- Adhesive tape
- Gauze swabs
- pH indicator sticks and/or electronic pH meter
- 1x Luer-lock blind end cap
- Gloves & apron
- Stethoscope
- Tray
- Wheeled trolley
- Glass of water (only for conscious patients with an intact gag reflex)

Table 6.2: Equipment necessary for NJ tube insertion



(a) **(b)** **(c)**

Figure 6.2: Method of NJ tube insertion. Figure (a) demonstrates oesophageal placement to 35-40 cm (dashed line). Figure (b) demonstrates the NJ tube tip in the stomach at a depth of 60 cm (dashed line). Figure (c) demonstrates the progressive insertion of the feeding tube at 5 cm intervals (dashed lines) so that the tip passes the pylorus and comes to lie at approximately 115 cm as measured from the nostril. (Figures adapted from open source internet images from the following websites www.wikipedia.org and www.mydr.com.au).

Gastric placement (Figure 6.2b): Following successful oesophageal intubation, the tube was advanced into the stomach, as guided by measurements taken prior to tube insertion. This level invariably lay at between 55 and 65cm as measured from the tip of the nostril. Starting at 40cm, aspiration was attempted at 5cm intervals till the required position was established. Aspiration with a 20 cc syringe was attempted three times at each level. Air insufflation and patient turning were employed if aspiration failed.

Confirmation of gastric placement was again performed using the 'whoosh test', and then by instilling and reaspirating 100ml of air. This latter 'vacuum test' manoeuvre (Welch *et al*., 1994) is possible only in the large volume of the stomach. Any fluid aspirate was tested for pH, and assessment for coiling was also performed using the guide wire.

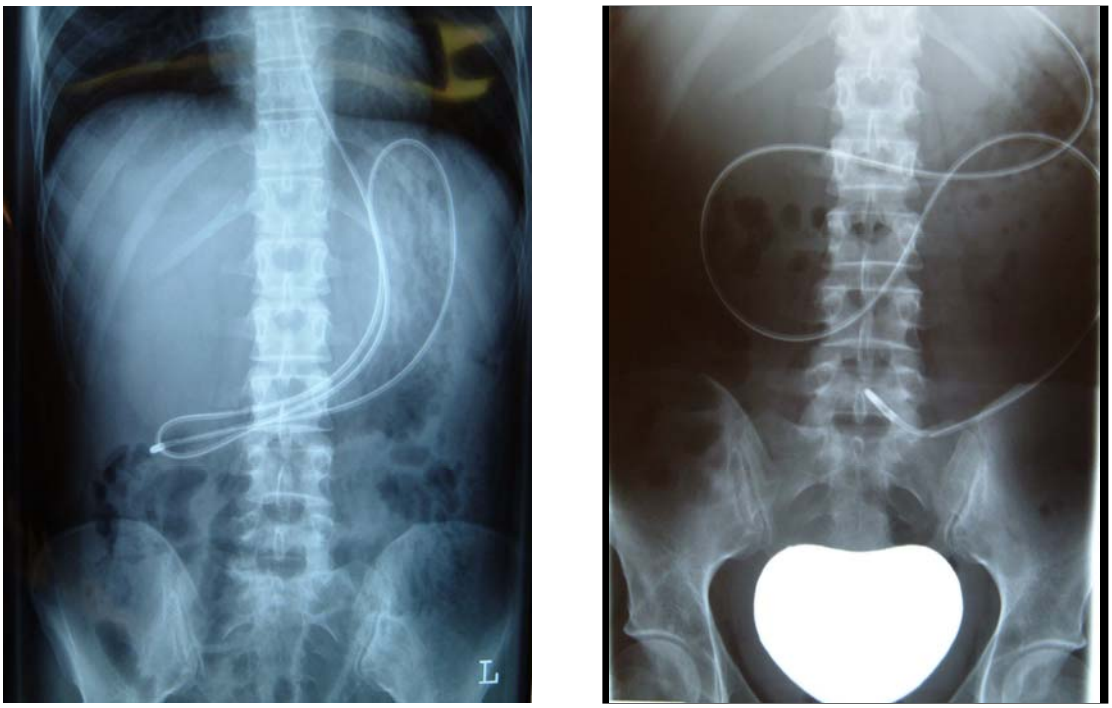
Postpyloric placement (Figure 6.2c): Once gastric tube placement was confirmed, postpyloric placement was achieved by advancing the tube at 5cm intervals and checking its position at each stage. In this manner, the tube was advanced to 115cm such that the tube tip lay at or beyond the DJ flexure. Placement was checked at each 5cm once again by the insufflation of 100 ml of air which resulted in a minimal return of air on aspiration (usually <20ml using a 20 cc syringe) once the tube had passed the pylorus (the vacuum test; Welch *et al*., 1994). This probably occurs because the relatively low volume duodenum collapses against the tube once negative pressure is applied, preventing any residual air from being withdrawn. Any fluid aspirate obtained was also checked for pH. However the most useful information with regards to correct placement was gleaned from the guide wire.

The main difficulty encountered at this stage was coiling of the tube in the stomach (Figure 6.3a). In a coiled tube, an indwelling guide wire can be withdrawn with ease, but not readvanced without some force (Slagt *et al.*, 2004). Learning to detect this subjective 'catching' sensation is a fundamental part of the learning curve for this technique as it suggests coiling, and indicated the need to withdrawn the tube back to 55 cm for further attempts at pyloric intubation.

Once the required position was achieved, the tube was secured to the nose with adhesive tape, and correct placement was confirmed radiologically prior to starting the feed (Figure 6.3b). X-rays were interpreted by two consultant radiologists and placement of the tube tip at different levels was recorded as lying at the level of 'D1, D2, D3 or D4' if placed respectively within the first, second, third or fourth part of the duodenum, 'DJ' if the tube tip lay at the duodeno-jejunal flexure, or 'beyond DJ' if the tube was placed in the small bowel beyond the DJ flexure.

6.4 RESULTS OF EMPLOYING THIS TECHNIQUE

32 patients (22 males, 10 females) with a median (IQR) age of 64 (59 - 74) years were recruited. Additional patient characteristics are summarised in Table 6.3. A total of 43 postpyloric tubes were inserted to a median (IQR) of 115 (94-115) cm as calculated from the ipsilateral nostril.



(a) **(b)**

Figure 6.3: Plain abdominal x-rays showing an NJ tube which has coiled in the stomach (a), and one where the tip is positioned beyond the DJ flexure (b). The latter also demonstrates the classical C-shaped duodenal configuration diagnostic of postpyloric placement. Radiographs are reproduced with the consent of patients from this study.

Variable	Value
Patients	32
Number of NJ feeding tubes placed	43
Postpyloric placement (%)	35 (81%)
Demographics	
Age (years) *	64 (59 - 74)
Sex ratio (M : F)	22 : 10
BMI	26.3 (22.0 - 31.1)
APACHE II score *	13 (6 - 19)
Patients on acid suppressing medications (%)	25 (78%)
Patients on intensive care during feeding (%)	24 (75%)
Patients on ventilation during feeding (%)	17 (53%)
Length of hospital stay (days)	28 (12 - 48)
Nutritional data	
Daily nutritional requirements (kcal / 24h)	1576 (1498 - 1834)
Length of feeding (days)	7 (6 - 14)
Diagnosis being treated (%)	
Post-operative	11 (34%)
Colorectal resection / peritonitis	8
Perforated peptic ulcer	2
Ruptured abdominal aortic aneurysm	1
Pancreatitis	9 (28%)
Sepsis / Multiorgan failure	5 (16%)
Polytrauma	4 (13%)
Other	3 (9%)

Table 6.3: Patient characteristics and indications for feeding

* values are median (IQR)

81% (35/43) of NJ tubes were successfully placed postpylorically, 7 (16%) coiled in the stomach, and one tube was placed intrabronchially, as judged radiologically. The latter occurred in a mechanically ventilated patient. None of the 7 tubes that coiled in the stomach spontaneously passed postpylorically on subsequent X-rays. Of the 35 (81%) tubes successfully positioned postpylorically, 30 (70% of all NJ tubes) were placed at or beyond the duodeno-jejunal (DJ) flexure as determined by plain abdominal x-rays. Of the remainder, 3 (7%) were placed in D2, 1 (2%) tube tip was in D3 and 1 (2%) was in the 4th part of the duodenum, just proximal to the DJ flexure. At completion of feeding, none of the postpyloric tubes had displaced back into the stomach.

Gastric fluid aspirates were obtained from 26/43 (60%) intubations. A gastric aspirate pH of $\leq$5 was obtained in 19/43 (44%) intubations while a pH of >5 was obtained in 7/43 (16%) intubations. A postpyloric aspirate was obtained in only 2 of 35 (6%) successful postpyloric intubations. 35/43 (81%) of all intubations were in patients receiving acid suppressing medications (25/32 (78%) of all patients). Radiology easily demonstrated the position of the tube tip in all cases (Fig. 6.3).

The median (IQR) time necessary for tube insertion was 18 (14 - 30) minutes. Using this technique of bedside postpyloric tube placement, it was possible to start EN at a median (IQR) of 6 (5 - 18) hours from the decision to feed. Median (IQR) visual analog pain scores on tube insertion were 43 (28-67) which decreased to 17 (7-24) after 24 hours ($p<0.001$). These discomfort scores are represented graphically in Figure 6.4.

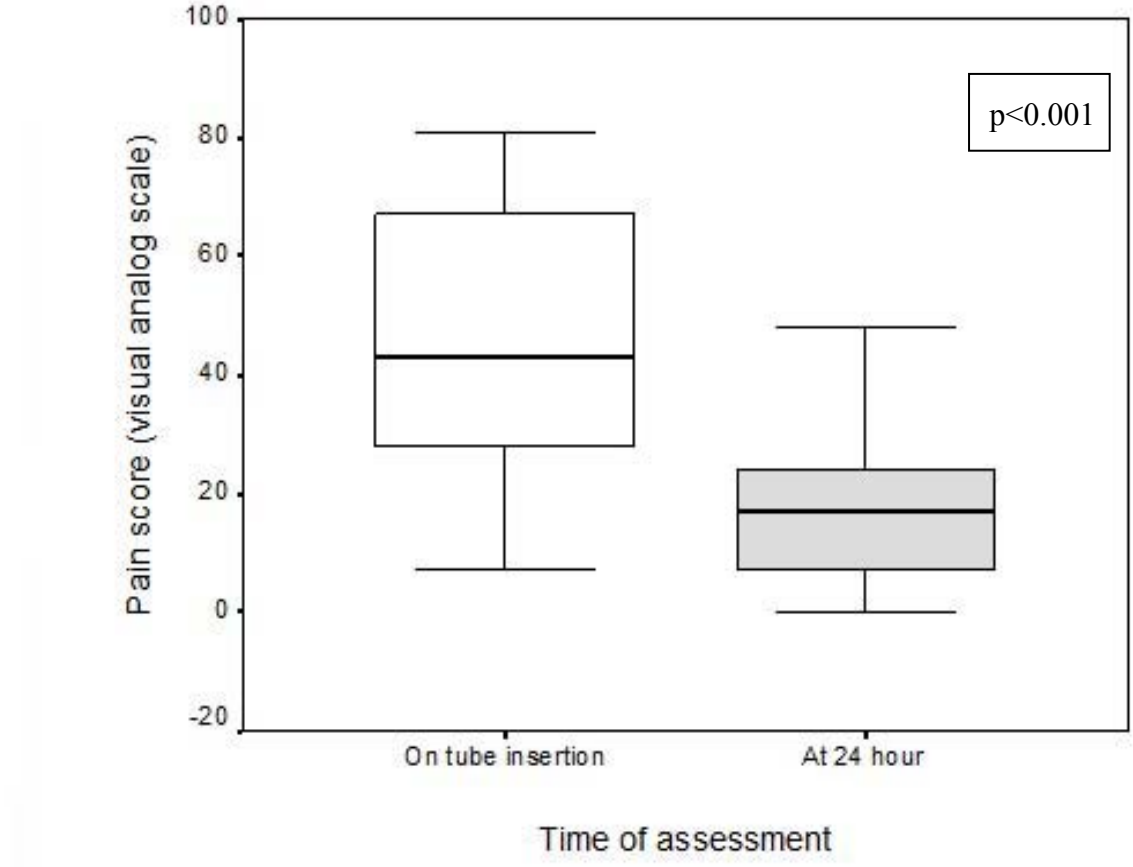


Figure 6.4: Comparison of visual analog pain scores for NJ tube insertion (43 [28 - 67]) and then one day later (17 [7 - 24]; p<0.001). The range of possible pain scores varied from a minimum of 0 to a maximum of 100.

6.5 DISCUSSION

The results of this study indicate that by-the-bedside postpyloric tube placement using this novel blind technique is usually successful. Although NJ tube placement takes longer to achieve than NG tube insertion, this difference is insignificant when compared to the cumulative time necessary both to organize and to insert NJ tubes by endoscopy or radiology. Findings from this study also suggest that the reliance on enteric aspirate pH to confirm feeding tube position is limited by low aspirate yields through fine bore tubes.

In developing this technique the investigators wished to devise a method which would allow for blind bedside placement with a high degree of success. It was also felt that such a technique should not require specialized equipment, incur any increases in cost, or indeed necessitate patient transfer. Blind by-the-bedside postpyloric tube placement has been described before, with varying degrees of success (Thurlow, 1986; Lord *et al*., 1993; Salasidis, Fleiszer and Johnston, 1998; Ahmed *et al*., 1999). The technique described in this study was put together after an extensive literature review and incorporates both novel practices as well as elements of previously described techniques. Laryngoscopy was used to confirm oesophageal placement of tubes in ventilated patients. This innovation was incorporated into the tube-insertion protocol following inadvertent intrabronchial intubation in one such ventilated patient. The literature suggests that patients with an indwelling endotracheal tube, far from being protected from intrabronchial placement, are in fact those most at risk from this complication (Marderstein, Simmons and Ochoa, 2004).

There is a learning curve for insertion of such tubes. The researcher in question had no prior experience of inserting NJ tubes such that the learning process is integrated in the study results. Further, confirmed failure to achieve postpyloric placement was not followed by reattempts at correct placement if the NJ tube was coiled in the stomach on radiography. In the absence of definitive evidence in favour of postpyloric feeding, this was deemed as unnecessary distress to patients. For both these reasons, it may be speculated that the results of this study may actually underestimate the true success of this technique.

Postpyloric tubes took a median of 18 minutes to be inserted and were successfully placed beyond the pylorus in 81% of cases on the first attempt. This compares favourably with other similar techniques described in the literature, including radiological, endoscopic and in particular, other blind methods of tube insertion (Shipps *et al.*, 1979; Thurlow, 1986; Rives *et al.*, 1989; Lord *et al*., 1993; Hillard *et al*., 1995; Hernandez-Socorro *et al*., 1996; Salasidis, Fleiszer and Johnston, 1998; Ahmed *et al*., 1999). The authors recognise that the delay of 6 hours to the instigation of feeding was primarily introduced by the study design which necessitated radiological confirmation of tube tip position prior to the commencement of feeding. This interval overestimates the actual delay necessary to instigate feeding outside the remits of a study and when tube tip position can be confirmed clinically without the need to rely on radiology.

The procedure of nasoenteral feeding tube insertion is uncomfortable to patients. Discomfort persists even once the tube is in place, but this decreases significantly with

time. To the authors' knowledge, this is the first study of its kind to attempt to quantify this endpoint and highlights the need to regularly reappraise the need for adjuvant nutritional support by means of nasoenteral tubes as this is distressing to patients. Metoclopramide was used in all patients, with no adverse complications associated with its use in agreement with other reported studies, even though its value remains somewhat contentious (Rhoney *et al.*, 2002; Heyland *et al*., 2004; Nursala *et al.*, 2007).

While most trials have shown no difference in the transpyloric passage of different fine-bore feeding tubes (Levenson *et al.*, 1988), a study by Lord *et al.* (1993) comparing weighted and non-weighted tubes showed a distinct advantage in favour of non-weighted tubes. Rees, Payne-James and Silk (1988) have further shown that non-weighted tubes stay in position for longer than their weighted counterparts, with a decreased propensity of the former to dislodge back into the stomach despite costing less. For these reasons, non-weighted tubes were used throughout in this study. None of the NJ tubes successfully placed beyond the pylorus spontaneously dislodged back into the stomach. This suggests but does not prove that the phenomenon of spontaneous tube dislodgement back into the stomach may be tube-type dependent and highlights the importance of selecting good feeding tubes made of quality materials. Further studies are however necessary to make definitive conclusions in this respect.

Much has been written in both the medical literature and the lay media about adverse outcomes following malpositioning of fine bore feeding tubes. Most authorities, particularly those in the United Kingdom, now recommend the use of pH in favour of

other techniques to establish tube placement (MHRA, 2004; NPSA, 2007). In this study, gastrointestinal placement of the feeding tube was confirmed by a combination of techniques. These included the use of direct laryngoscopy to ensure oesophageal placement in ventilated patients, the insufflation of air with auscultation in the epigastrium (the 'whoosh' test) for placement in the stomach and / or duodenum, the reaspiration of insufflated air (the vacuum test) to differentiate pre- from postpyloric position, pH measurements of fluid aspirates as well as a confirmatory radiograph. An indwelling guide wire was also used to ensure that the tube was not coiled, but provided no further information as to the position of the tube tip.

Previous studies report an 80-85% PPV of the 'whoosh test' to confirm the position of nasoenteral tubes in the stomach or the duodenum (Welch *et al*., 1994). However other publications have questioned the accuracy of this technique (Stroud, Duncan and Nightingale, 2003; MHRA, 2004; Seguin *et al*., 2005; NPSA, 2007; Elpern *et al*., 2007). Similarly, the low NPV of the 'vacuum test' to confirm duodenal placement limits its discriminating value (Welch *et al*., 1994). The determination of fluid aspirate pH has been reported to be very effective in predicting the placement of tubes within the gastrointestinal tract since an acidic pH of 4 to 5 is diagnostic of gastric placement. A conservative approach was taken in this study given that 78% of patients were on acid suppressing medications, such that a pH of $\leq$5 was taken to indicate gastric placement (Phang *et al*., 2004). A prepyloric fluid aspirate was only obtained in 60% of all intubations with only 44% showing a gastric pH $\leq$5. This observation question the advice currently being circulated which encourages the use of gastric aspirate pH in

preference to other techniques for confirming gastrointestinal tube placement. The evidence from his study suggests that this will only yield reliable information in less than half of intubations. Given the potentially lethal consequences of feeding into the lungs, the authors are of the opinion that no single test should be used to confirm gastrointestinal placement. It is felt that the reliability of multiple tests together with a conscious interpretation of their findings should be encouraged.

In conclusion, this study confirms that it is possible to place postpyloric tubes blindly by the bedside in the majority of patients requiring adjuvant enteral nutritional support. Incorporation into this protocol of newer technologies which provide real-time by-the-bedside visual feedback of the tube tip location, may further improve the success rate and decrease the time necessary to achieve NJ placement (Gabriel and Ackermann, 2004; Young *et al*., 2005; Phang, Marsh and Prager, 2006). By employing successful bedside techniques of postpyloric tube placement, one may pursue randomized feeding studies without bias relating to difficulty of establishing tube placement. This may allow one to answer the pertinent question of whether the site of nutrient delivery influences the enteral tolerance of feeds, or whether this is more a function of underlying gut function itself and will be pursued in the next study.

6.6 A RANDOMIZED CLINICAL TRIAL TO ASSESS THE IMPORTANCE OF THE SITE OF FEED DELIVERY ON ENTERAL TOLERANCE: INTRODUCTION

Controversy persists as to the respective roles of pre and postpyloric feeding. Prepyloric or intragastric feeding is safe, easy to establish and permits early commencement of EN. A major drawback, however, is a high incidence of enteral intolerance which many assume to be related to varying degrees of gastroparesis or gastroduodenal dysmotility, particularly in the critically ill (Ritz *et al*., 2000; Mentec *et al*., 2001; Davis *et al*., 2002; Heyland *et al*., 2004, Binnekade *et al*., 2005). Not surprisingly, therefore, many authorities advocate the use of postpyloric feeding, which, it is argued, is associated with improved tolerance and less frequent bloating, nausea, vomiting or aspiration (Montecalvo *et al.*, 1992; ASPEN, 2002). However, the inconsistency of the literature has led some to doubt these and other claimed benefits of postpyloric feeding (Marik and Zaloga, 2003; Kreymann *et al*., 2006; Ho, Dobb and Webb, 2006; McGuire and McEwan, 2007). Further, there is increasing concern that the use of jejunostomies is often associated with a delay in the instigation of feeds and are themselves occasionally associated with significant morbidity (Zapas, Karakozis and Kirkpatrick, 1998; Abou-Assi, Khurana and Schubert, 2005).

There are many possible reasons for the discrepancies in published results. Firstly, protocols for delivery of enteral nutrients are variable, secondly, there is little agreement as to the primary end point that needs to be measured, and thirdly, an unavoidable bias is

introduced into most studies as a consequence of inevitable delays that occur in establishing postpyloric access. A randomised clinical trial was set up to readdress these issues. For purposes of this trial, the authors developed and validated a bedside technique for postpyloric tube placement (section 6.2 - 6.5) in an attempt to eliminate bias relating to the difficulty in attaining postpyloric tube access.

The primary end point of this prospective trial was to determine whether or not the site of feed delivery (pre or postpyloric) influenced the number of patients who achieved 'enteral tolerance'. Enteral tolerance, for the purposes of this study, was defined as the ability to tolerate $\geq$80% of prescribed intakes for a minimum continuous period of 48 hours. Secondary end points included measurements of the time required to initiate feeding, as well as to achieve goal feed rates and tolerance, the adequacy of calorie intakes between groups, morbidity and mortality, and an assessment of the accuracy of methods used to establish tube position.

6.7 METHODS

This study was approved by the Scarborough LREC (Ref. No. PB/rh/03/313). All patients referred for EN were eligible for entry into this study. Exclusion criteria included failure to obtain consent, intolerance to intubation, age <18yrs, pregnancy and those patients deemed to have IGF necessitating supplemental PN. Patients were randomized by means of lists of randomly generated numbers to receive prepyloric feeding via a NG tube, or

postpyloric feeding via a NJ tube. NG or NJ tubes were converted to percutaneous gastrostomies (PEG) or percutaneous endoscopic gastrojejunostomies (PEGJ) respectively if clinically appropriate to the individual patient.

All patients receiving nutritional support in Scarborough Hospital are managed by a multidisciplinary hospital nutrition team. EN is employed whenever possible and feeds are established according to a strict feeding protocol which includes the routine use of metoclopramide. CORFLO® Fr 8 fine bore feeding tubes (Merck Pharmaceuticals, Windsor, Berkshire, UK) which were 92 or 140 cm long, were used respectively for NG or NJ intubation. Freka® Fr 15 tubes (Fresenius Kabi AG, Bad Homburg, Germany) were used as PEGs. A Fr 9 intestinal tube (Freka® Intestinal Tube Fr 9 for PEG Fr 15, Fresenius Kabi AG, Bad Homburg, Germany) was used to establish PEGJ feeding. All feeding tubes (NG and NJ) were placed by the bedside by the same individual using the technique described in section 6.3.2.

All other members of the nutrition team as well as the attending clinical staff were blinded to the results of randomization throughout the study period. Radiological confirmation of tube tip placement was performed in all patients prior to the commencement of feeds, at weekly intervals thereafter, and where possible at the termination of feeding prior to tube removal. A baseline chest X-ray was also performed prior to the commencement of feeds. All X-rays were kept separate from the patient and were reported without referring to the tube tip position in an effort to assist blinding. For this purpose, reports of tube tip position were only forwarded to the primary investigator.

All patients received the prokinetic metoclopramide via the intravenous route in a dose of 10 mg three times a day for the duration of feeding unless medically contraindicated or side-effects developed. Nutritional requirements were calculated using measurements of body weight in conjunction with standard tables (appendix 4). These estimates were used to establish a goal rate for each patient. A commercially available 1kcal/ml fibre-free tube feed (Fresubin® original, Fresenius Kabi AG, Bad Homburg, Germany) was used in all patients. The constitution of this feed is summarised in appendix 5.

Enteral feeding was managed according to a standard protocol. All feeds were commenced at 20 ml/hour. Subject to tolerance and gastric residual volumes (GRV) of less than 200 ml, this was followed by 4 hourly increments of 20 ml/hour until goal rate was achieved. Feeding occurred over 20 hours in each 24 hours with a four hour feed break. GRV were assessed 4 hourly during feed build-up or more frequently if patients developed symptoms of intolerance. Once goal rates were achieved, GRVs were then assessed 6 hourly for the duration of feeding. Patients were reviewed twice daily until discharge or death.

6.7.1 End points recorded

All end points were recorded prospectively. The primary outcome measure was the ability to achieve enteral tolerance. This was defined as the ability to achieve at least 80% of the prescribed intakes (i.e. $\geq$80% of goal feed rate) for a minimum continuous period

of 48 hours. Secondary outcome measures included recording the time in hours necessary to achieve the goal rate (hourly targeted intake), duration of feeding, calorie intakes and all morbidity. In addition, the time (in hours) necessary to instigate feeding from the decision to feed was also recorded.

Complications were classified as feed or tube related complications, septic complications and in-hospital deaths. Septic complications were defined as the presence of recognised pathogens in normally sterile body tissues or fluids, confirmed by culture and supported by clinical, haematological and/or radiological evidence. All complications were recorded from the time of recruitment till discharge from hospital or patient demise.

Aspirate pH obtained during tube insertion was assessed using Multistix® 10 SG (Bayer Diagnostics Mfg., Ltd. Bridgend, UK) reagent strips and confirmed using an electronic handheld pH meter (Hanna pH tester, Progen Scientific Ltd, Mexborough, UK) which was regularly calibrated as recommended by the manufacturer and which gave digital pH readings between the pH of 0 and 14 to the closest two decimal points. A pH of $\leq$5 was considered to indicate gastric placement (Phang *et al*., 2004).

The success of by-the-bedside post-pyloric tube placement was confirmed by radiology and was recorded. In the case of failed postpyloric placement, no further attempts were made to adjust the position of the tube and data handling was conducted on an 'intention to treat' basis.

6.7.2 Statistical analysis

Based on published data (Woodcock *et al*., 2001), a sample size calculation showed that a minimum of 32 patients would be required in each group in order to demonstrate a reduction in enteral intolerance to 30% at the 5% level of significance with a power of 80%. Results from the study were tabulated on an Excel® spreadsheet (Excel for Windows®, Microsoft Corporation, Redmond, Washington, USA) and then analysed using SPSS® for Windows® version 11.5 (SPSS®, Chicago, Illinois, USA). Continuous variables were expressed as medians (IQR). Continuous variables were compared with the Mann-Whitney *U* Test for non-parametric variables and relationships between groups were assessed using χ^2 test for binary outcomes or Fisher's exact test for small cohort as appropriate. Statistical significance was considered at the 5 percent level and data was analysed on an 'intention to treat' basis.

6.8 RESULTS: THE IMPORTANCE OF THE SITE OF FEED DELIVERY

Of 103 eligible patients, 29 were excluded because of an inability to obtain consent and 9 as a result of feeding tube intolerance. A total of 65 patients were finally recruited to the trial (M:F of 41:24; median (IQR) age of 66 (57-76) years) and followed up for a total of 658 (359 prepyloric *versus* 299 postpyloric) patient feeding days. There were 33 patients randomized to prepyloric and 32 to postpyloric feeding. Three patients in the prepyloric group required conversion to PEG feeding and 4 in the postpyloric group had a PEGJ

inserted (p=0.964). Table 6.4 summarises the demographic data of the two groups which were comparable with respect to age, sex ratios, height, weight, BMI, length of feeding, goal feed rate, prevalence of diabetes and malignancy, as well as disease severity as assessed using APACHE II scoring. The reasons for feeding are summarised in Table 6.5. All except 2 patients, one from each group, received metoclopramide. In one patient, metoclopramide was withheld because of previously reported hypersensitivity while the second patient had severe Parkinson's disease. There were no recorded side-effects from the use of this prokinetics in this study.

Overall, enteral tolerance was achieved in 66% (n = 43) of patients in this study. There was, however, no significant difference between the groups in this primary end-point (p=0.539). Enteral tolerance was achieved in 23/33 (70%) patients in the prepyloric group compared to 20/32 (63%) patients in the postpyloric group. In these patients who did achieve enteral tolerance (23 and 20 patients in the two groups respectively), this was achieved significantly more rapidly in patients in the postpyloric group (83 (66-207) hours *versus* 67 (63-87) hours, p=0.024).

With the implementation of a bedside technique of postpyloric tube placement, no differences were observed between groups in the time necessary to instigate feeding from the clinical decision to institute EN (prepyloric, 8 (5-17) hours *versus* postpyloric, 7 (5-22) hours; p=0.896). Similarly, patients in both groups achieved their goal feeding rates in comparable times from feed initiation (22 (15-85) hours *versus* 20 (16-24) hours respectively; p=0.203).There was no significant difference between the groups in the

	Prepyloric feeding	Postpyloric feeding	p-value
Patients (Total = 65)	33	32	-
Demographics			
Age (years) *	67 (60-79)	64 (57-72)	0.213†
Sex ratio (M : F)	20 : 13	21 : 11	0.675‡
Height (meters) *	1.67 (1.61-1.75)	1.70 (1.66-1.78)	0.188†
Weight (kg) *	71.0 (60.8-77.9)	76.3 (64.6-89.2)	0.088†
BMI *	25.7 (22.1-28.3)	25.5 (21.8-30.1)	0.443†
Nutritional data			
Total days of feeding * (days)	359	299	-
Median length of feeding * (days)	8 (4-14)	6.5 (5-13)	0.665†
Target feed rate * (ml/hr)	75 (70-80)	75 (75-90)	0.142†
Median daily nutritional requirements * (Kcal/day)	1513 (1401-1608)	1519 (1486-1798)	0.285†
Median daily feed delivery * (Kcal/day)	1298 (1138-1483)	1249 (1066-1486)	0.837†
Overall calories delivered* (Kcal)	12104 (4464-17593)	9120 (5221-17412)	0.501†
Patients achieving $\geq$80% of total requirements (%)	23 (70)	20 (63)	0.539‡
Patients requiring PEGJ / PEG (%)	3 (9)	4 (13)	0.964§
Indicators of outcome			
Patients with diabetes (%)	5 (15)	5 (16)	0.957‡
Patients with malignancy (%)	3 (9)	1 (3)	0.636§
Patients requiring surgery (%)	18 (54)	14 (44)	0.384‡
Patients requiring ventilation (%)	16 (48)	13 (41)	0.451‡
Patients requiring inotropes (%)	13 (39)	11 (34)	0.469‡
Patients on ICU (%)	21 (64)	19 (59)	0.724‡
APACHE II score *	13 (11-16)	13 (5-17)	0.573†

Table 6.4: Comparison of groups and patient demographics.

(* median (IQR); § Fisher's exact test; ‡ χ^2 test; † Mann-Whitney *U* Test)

	Prepyloric feeding N=33	Postpyloric feeding N=32
Primary diagnosis treated		
Postoperative†		
Peritonitis / obstruction	4	6
Trauma / Orthopaedic	3	3
Peptic ulcer disease	1	2
Aneurysm surgery	2	1
Oesophageal perforation	1	0
Upper gastrointestinal pathology		
Acute severe pancreatitis	3	5
Pancreatic mass	0	2
Dysphagia	2	0
Obstructive jaundice	1	0
Sepsis / Organ failure		
Generalized sepsis / shock	6	4
Chest infections / COPD exacerbation	4	3
Liver failure / encephalopathy	3	1
Stroke	2	1
Miscellaneous	1	4
Reason for feeding		
Intubated and ventilated	16	13
Inadequate oral intake	9	11
Pancreatitis	3	5
Dysphagia / unable to swallow / absent gag	4	1
Other	1	2

Table 6.5: Clinical information relating to the main diagnosis treated and the reason for instituting adjuvant feeding. († 32 patients underwent surgery, but only 23 were fed as a direct result of having had a surgical intervention.)

median duration of feeding (prepyloric, 8 (4-14) days *versus* postpyloric, 6.5 (5-13) days; p=0.665). and the total calories received (p=0.501). The proportion of feed actually administered in relation to the total requirements for the same time period was also comparable (p=0.847).

There were no differences between the groups with respect to recovery time, complications or mortality (Table 6.6). High gastric residual volumes (GRV) necessitating the alteration or cessation of feeding occurred more frequently in patients fed prepylorically (9 *versus* 1 respectively; p=0.014). High GRV were positively associated with vomiting (p=0.003), but neither high GRV nor the documentation of vomiting during the feeding period were associated with the development of new onset pneumonia. Similarly, the presence of high GRV necessitating feed alteration was not associated with the ability or otherwise of patients to ultimately achieve enteral tolerance.

All tubes were readily visible on plain radiology, and all were placed in the alimentary tract. A fluid aspirate for pH estimation was obtained from 32/65 (49%) patients, with 22 (33%) aspirates showing an acidic pH confirming gastric placement or passage. 82 per cent of patients randomized to postpyloric feeding had successful postpyloric intubation. In the postpyloric group, none of the successfully placed tubes dislodged back into the stomach over the course of the study. Similarly, none of the NJ tubes that coiled in the stomach were propelled postpylorically with time. Two of the 4 PEGJ tubes were found to be coiled in the stomach on radiology at 1 week after insertion.

	Prepyloric feeding N=33	Postpyloric feeding N=32	p-value
Patients developing one or more complications (%)	29 (88)	27 (84)	0.683‡
Patients with tube related complications	21 (64)	18 (56)	0.543‡
Tube blockage	5 (15)	5 (16)	0.957‡
Tube dislodgement	16 (48)	15 (47)	0.897‡
1 dislodgement	9	9	-
2 dislodgements	6	6	-
≥3 dislodgements	1	0	-
Abrasions/erosions/bleeding	6 (18)	4 (13)	0.773§
Patients with feed related complications (%)	16 (48)	11 (34)	0.248‡
High GRV necessitating changes to feeding (%)	9 (27)	1 (3)	**0.015**§
Vomiting	7 (21)	5 (16)	0.561‡
Diarrhoea	5 (15)	7 (22)	0.485‡
Bloating / Distension	2 (6)	6 (19)	0.238§
Patients with new septic complications (%)	8 (24)	2 (6)	0.092§
New onset pneumonia	7 (21)	1 (3)	0.060§
Bacteraemia	4 (12)	2 (6)	0.702§
Urinary tract infection	2 (6)	0 (0)	0.507§
Subphrenic collection	0 (0)	1 (3)	0.984§
Outcome			
Patients achieving enteral tolerance (%)	23 (70)	20 (63)	0.539‡
Length of ICU stay in days *¥	14 (8-24) ¥	8 (5-23) ¥	0.283†¥
Overall hospital stay in days *	34 (20-79)	25 (16-45)	0.100†
Death (%)	11(33)	6 (19)	0.181‡

Table 6.6: Complications and outcomes.

(* median (IQR); ¥ where relevant / subgroup analysis; ‡ χ^2 test;

§ Fisher's exact test; † Mann-Whitney *U* Test)

6.9 DISCUSSION: THE IMPORTANCE OF THE SITE OF FEED DELIVERY

The results of this randomized clinical study indicate that the delivery of nutrients beyond the pylorus is not associated with any improvements in the patient's ability to achieve enteral tolerance compared to prepyloric administration. In those patients who did achieve tolerance, however, postpyloric feeding did permit more rapid attainment of goal rates and was associated with a reduced incidence of high gastric residual volumes. However, this was not associated with significant differences in nutritional intakes, enhanced recovery or incidence of complications.

A major drawback to postpyloric nutrition is the need to establish jejunal access (Davis *et al*., 2002; Heyland *et al*., 2004). This often necessitates endoscopic or fluoroscopic assistance which may result in significant delays in the instigation of feeds. Failure of published randomized trials to correct for this anomaly constitutes a bias which favours postpyloric feeding. This hidden bias may account for some of the inconsistencies in the literature relating to the perceived benefits of postpyloric feeding; benefits which are not appreciated in daily clinical practice as they do not really exist. Bedside techniques similar to the one employed in this study eliminates this problem by ensuring that instigation of feeding occurs in comparable times irrespective of the site of feed delivery. The technique of NJ tube placement employed in this study has been previously validated by the authors (sections 6.2 - 6.5) and has a success rate in the order of 81% which compares favourably with radiological, fluoroscopic and other blind techniques of postpyloric intubation (Shipps *et al.*, 1979; Thurlow, 1986; Rives *et al.*, 1989; Lord *et*

al., 1993; Hillard *et al*., 1995; Hernandez-Socorro *et al*., 1996; Salasidis, Fleiszer and Johnston, 1998; Ahmed *et al*., 1999).

As a result of the perceived difficulties in establishing jejunal access, many advocate the use of percutaneous jejunostomies placed radiologically or at the time of abdominal surgery (Kreymann *et al*., 2006). These allow early feeding and there is good evidence to show that their use permits early achievement of goal rates (Kreymann *et al*., 2006). However, these and other percutaneous techniques of establishing feeding are not without serious potential complications such as intestinal obstruction, dislodgement and leaking around the tubes, resulting in peritonitis (Díaz de Liaño *et al*., 2005; Khan *et al*., 2008). In the absence of proven benefits for postpyloric feeding, their routine use is difficult to justify. The adoption of bedside techniques for establishing NJ tubes obviates the need for most percutaneously placed jejunostomies with their attendant risks.

The setting for this study was a busy district general hospital. Strict feeding protocols are implemented locally. These protocols adhere to international feeding guidelines and determine the indications for, and nature of, nutritional support therapy. Consecutive patients requiring EN were recruited. As such, the author considers the case mix of patients entered into this study to be representative of the majority of patients who may require EN in general hospital in the UK. It is noteworthy that the majority of patients were critically ill on the intensive care unit (ICU). As a result of the breadth of patients included, we recognise that our findings may not be directly applicable to certain sub-groups of patients such as the critically ill or those with confirmed gastric outlet

obstruction but otherwise normally functioning intestinal tracts.

It could be argued that results from this study favour prepyloric feeding on the basis that a high success with meeting requirements was achieved overall. In this study 66% patients were adequately fed, and was achieved through a dedicated multidisciplinary nutrition team adhering strictly to feeding management protocols which included the routine use of prokinetics drugs. These results compares very favourably with reported figures in the literature which frequently cite failure to achieve targeted intakes in up to 60% of patients receiving EN (Woodcock *et al.*, 2001).

In contrast to other trials comparing gastric and small bowel feeding, the primary endpoint of this study was enteral tolerance. This was assessed by strict criteria based upon observed intakes over time recorded by trained dieticians. Based upon the work presented in chapters 4 and 5, a cut-off point of 80% of prescribed calories for a minimum of 2 days was adopted to indicate 'tolerance'. It has been previously shown that this measure of enteral tolerance is reproducible and independently predicts outcome. In the author's view, use of this end point is preferable to using unvalidated markers such as gastric residual volumes as surrogate measures of tolerance. Other authors have also concluded that gastric residuals are not indicative of tolerance (Zaloga, 2005; McClave *et al*., 2005). Findings from this study support this because while gastric residuals were greater in patients fed nasogastrically, this did not equate with reduced tolerance. The assumption is often made that such reductions in gastric residuals may be associated with a reduced incidence of aspiration pneumonia. We and others have been unable to

demonstrate any effect on pneumonia confirming results of studies using radioisotopes which do not show increased risks of aspiration with gastric feeding or commensurate reductions with post-pyloric feeding (Lull *et al*., 1980; Heyland *et al*., 2001[a]). Similarly, there is no evidence to confirm that changes in GRV equate with tolerance (Zaloga, 2005; McClave *et al*., 2005). It is likely, therefore, that differences in gastric residuals simply reflect ease of aspiration related to tube position. The results of this study would suggest that management protocols for EN that are based on the repeated measurement of gastric residual volume require reassessment.

In this study, there were no differences in tube related complications between groups. This included tube blockage, complete tube dislodgement, abrasions caused by the tubes, and the need for tube repositioning. Previous authors have commented upon the high incidence with which jejunal tubes recoil back into the stomach with time (Boulton-Jones, *et al*., 2004) and this has often been used as an argument against postpyloric feeding. A number of these studies, however, related to the use of PEGJ tubes or were limited to children. Radiological findings from this study confirmed that none of the NJ tubes successfully placed beyond the pylorus recoiled back into the stomach, however 2 of the 4 PEGJ tubes dislodged proximally. This suggests that postpyloric tube dislodgement may be tube type dependent but is probably infrequent after successful NJ tube placement. In addition, the importance of radiological confirmation of tube position was emphasised by the results of pH testing in this study. Fluid aspirates could be obtained in only 32/65 (49%) patients and these were acidic, confirming gastric placement or passage, in only 22 (33%) patients.

The most significant finding of this study is that administration of EN beyond the pylorus confers no advantage over gastric feeding with respect to enteral tolerance or the ability to achieve targeted intakes. This finding is in accord with many other studies. There is a growing consensus, based on a number of randomized trials and a few systematic reviews, that the site of delivery of EN has no influence on total caloric intake, lengths of intensive care or hospital stay, or enteral tolerance in the majority of patients (Marik and Zaloga, 2003; Kreymann *et al*., 2006; Ho, Dobb and Webb, 2006; McGuire and McEwan, 2007). Taken together these findings suggest that isolated gastroparesis or gastroduodenal dysmotility is unlikely to be a common reason for enteral intolerance. Whilst this may occur in selected subgroups, such as in patients with acute pancreatitis, it is probably uncommon and cannot be used as a justification for routine postpyloric delivery of nutrients. Enteral intolerance is probably a reflection of overall gastrointestinal function and not a consequence of isolated dysfunction of selected parts of the gut. A number of physiological studies support this contention. Dive *et al.* (Dive *et al*., 1994[a]; Dive *et al*., 1994[b]) studied migrating motor complexes (MMC) in the anthrum and proximal and distal duodenum of starved and enterally fed critically ill patients. This group was able to show that disruption in MMC could be detected at all three sites. In other words, the assumption that enteral intolerance may be largely due to an isolated gastroparesis, particularly in the critically ill, is probably inaccurate. The evidence suggests that enteral intolerance is more likely a result of 'overall' gastrointestinal dysfunction. It would be anticipated that such patients will not tolerate adequate EN irrespective of site of feed delivery, be that pre- or postpyloric.

Proponents of postpyloric feeding argue that early and aggressive EN is associated with improved clinical outcomes. These, it is said, occur as a consequence of meeting patients' nutritional requirements and maintaining the function and integrity of the gut. Early EN is particularly promoted in the care of burns patients and throughout the intensive care literature (Artinian, Krayem, and DiGiovine, 2006; Wasiak, Cleland, and Jeffery, 2006). The results of this study, and others, casts doubt on some of these assumptions. Our results show that postpyloric feeding does permit more rapid attainment of goal rates in the setting of a functioning gut, but this was not associated with any clinical improvements of significant overall calorie intakes. It is more probable that enteral tolerance itself is a reflection of underlying gut function. In those patients in whom there is no abnormality of gut function, tolerance will be achieved by whatever method of feed administration is employed.

This way of thinking allows for a new paradigm about the administration of adjuvant nutrition. This concept is that studies showing benefits from early EN show benefit not because of some ill defined mechanism relating to the act of EN or earlier attainment of some ill defined nutritional goal. Instead, improved outcomes relates to the fact that these patients have a normally functioning gastrointestinal tract allowing early enteral feeding to be instigated, and nutritional goals to be met. The same effect probably accounts for many of the perceived benefits of enteral over PN. Simply put, if patients are unable to tolerate EN thereby requiring parenteral feeding, this indicates gut failure which is itself a prognostic indicator. Given the numerous homeostatic roles of the gut over and above its nutritional function, including amongst others its barrier, immunological and hormone

producing roles, we feel this is a plausible conclusion and supports the theory that it is the state of underlying gut function or failure which is of prognostic significance, and not the method employed for feed delivery *per se*.

In summary, the site of enteral feed delivery appears to have little effect on overall tolerance in the majority of patients. There may still be a minority of patients in whom NG feeding may be inappropriate, such as those with gastric outlet obstruction, or the rare cases of isolated gastroparesis in whom the risks of regurgitation with intragastric feeding are substantial. Postpyloric feeding should probably only be instituted as a second-line method of enteral feeding where intragastric nutrition has failed, and in those units where intubation can be rapidly organised and instigated safely.

6.10 CONCLUSION

It is increasingly apparent that the ability of patients to achieve enteral tolerance probably relates more to the overall function of their gastrointestinal tract than to the site of enteral feed delivery *per se*. As such, when defining the state of gut function it is not essential to make allowance for the site of enteral feed delivery, be this pre- or postpyloric.

CHAPTER 7:

THE EFFECTS OF DIFFERENT MODALITIES OF FEEDING ON SUPERIOR MESENTERIC ARTERY BLOOD FLOW

'What is food to one, is to others bitter poison.'

Lucretius

96 BC - 55 BC

De Rerum Natura

7.1 INTRODUCTION: SPLANCHNIC PERFUSION AND FEEDING

Increasing awareness of the deleterious effects of malnutrition in hospitalized patients has led to earlier institution of adjuvant feeding (Jeejeebhoy, 2002; Dominioni *et al*., 2003). However, alterations in basic physiology brought about by such treatment modalities are poorly characterized. It is generally accepted that oral alimentation increases gastrointestinal blood flow (Moneta *et al*., 1988); but there is a relative paucity of data regarding the effects of adjuvant nutritional support, whether enteral or parenteral, on splanchnic perfusion in man.

Historically, measurements of changes in splanchnic blood flow have been difficult, relying on invasive assessment modalities (Ackland, Grocott and Mythen, 2000). This has resulted in a wealth of information from animal models, but for ethical and logistical reasons, data from humans has been shortcoming, and mostly inferred. The advent of non-invasive methods of flow assessment, and in particular Doppler ultrasonography (DUS), has made repeated non-invasive measurements of splanchnic flow easy, practical, and safe in humans. The primary aim of this study was to use DUS to assess qualitative changes in SMA flow associated with enteral and parenteral nutrition in patients requiring adjuvant feeding.

7.2 PATIENTS AND METHODS

This prospective 'before-after' study comprised 34 subjects of whom 14 were healthy volunteers and 20 were consecutive patients who were receiving nutritional support. Patients were all being treated on the ICU or general wards of the index institution. Five groups were identified and these are summarised in Table 7.1. The volunteers were divided into a control group who received no feed (CF), a group who ate a standard meal (CO), and a group who received EN (CE). The patients were grouped according to the method of feeding they were receiving (enteral, PE; parenteral, PT).

All subjects had a baseline SMA measurement performed using DUS at 9.00 am after an overnight fast from midnight and a second measurement was performed 3 hours later. A total of 3 volunteers were allocated to group CF and received no feeding. This group was used to assess reliability of the method. In group CO, 6 patients received a standard oral test meal (530kcal) immediately following the baseline measurement of SMA flow. Group CE volunteers (n=5) received EN. In these subjects, an 8Fr NG feeding tube (CORFLO®, Merck Pharmaceuticals, Leicester, United Kingdom) was inserted after baseline measurement of SMA flow and then a 60 ml/hour infusion of a commercially available 1 kCal/ml enteral feed (Osmolite®, Abbot Nutrition, Berkshire, United Kingdom) was administered for 2 hour. The feed was then discontinued and the second scan performed an hour later.

The same study protocol was followed for the 20 patients receiving adjuvant nutritional

Group	Individuals in each group	First assessment (9.00 am)	Intervention	Second assessment (12.00 pm)
1. Controls, Fasting (CF)	3	Fasting	None	Fasting
2. Controls, Oral (CO)	6	Fasting	Oral meal (530 kCal)	Postprandial
3. Controls, EN (CE)	5	Fasting	Enteral challenge (120 kCal)	Postprandial
4. Patients, EN (PE)	10	Fasting	Enteral challenge (120 kCal)	Postprandial
5. Patients, TPN (PT)	10	Fasting	Parenteral challenge (175 kCal)	Postprandial

Table 7.1: Summary of the five groups and their corresponding intervention.

support. All feeding was discontinued from midnight and a baseline scan performed at 9.00 am. Feeding was then recommenced for 2 hours. In the patients receiving EN (group PE) this was 60ml/hr of a 1 kcal/ml enteral feed (Osmolite®, Abbot, UK). For the 10 patients receiving PN (group PT) this consisted of a 125 ml/hour infusion of a commercially available 0.7 kCal/ml peripheral parenteral feed (Kabiven® peripheral 9, Fresenius Kabi Ltd, Cheshire, United Kingdom). As with volunteers, the second scan was not performed until after a one hour 'stabilisation' period with no feeding.

Recruitment of controls was on a voluntary basis. To be eligible for the study, volunteers had to be healthy and off any regular medications, while having none of the exclusion criteria listed in Table 7.2. Consecutive patients receiving only enteral or only parenteral nutrition and satisfying the inclusion criteria were eligible for the study. Commercially available adjuvant feeds, as mentioned previously, were used for this purpose. The decision with regards to the modality of feeding was made by the attending physicians and the local nutrition support team and was based on clinical grounds alone. Recruitment of patients to this study only occurred once patients had been established on their designated feed for a minimum of 24 hours. This study had the approval of LREC (Ref. No. PB/RH/345) and all subjects gave informed and signed consent.

7.2.1 Superior mesenteric artery flow assessments

To permit changes in SMA flow to be measured after the appropriate intervention, two

Inclusion Criteria	Exclusion Criteria
• On EN only or on parenteral nutrition only • Established on EN or TPN for ≥24 hours	• Unable to obtain consent • History of severe atherosclerotic disease • Previous aortic surgery • On inotropic support • Bowel ischaemia • Unable to identify SMA on DUS

Table 7.2: Inclusion and exclusion criteria.

(EN, enteral nutrition; TPN, total parenteral nutrition; SMA, superior mesenteric artery; DUS, Doppler ultrasound)

separate sessions of DUS assessments were recorded for each patient. These were at an interval of three hours from one another. All measurements were performed by a single consultant radiologist in an attempt to decrease observer bias (Perko and Just, 1993; Iwao *et al*., 1996). This individual was blinded to the assigned group and to the method of feeding employed. Volunteers and patients in whom the SMA could not be identified on DUS were excluded from the trial.

SMA flow measurements were performed using a multi-frequency 2.5 MHz probe and real-time spectral analysis on an HDI 5000 UltrasoundSystem (ATL Ultrasound, Bothwell, USA). SMA flow was measured at the proximal 1-2 cm segment of the SMA near to its origin from the aorta. Angle of insonation was maintained as low as possible to minimise errors in velocity calculations. All measurements were performed in the supine position after a minimum of 5 minutes rest to further minimise inaccuracies caused by physical exertion.

Each SMA flow measurement consisted of 3 time-velocity waveform readings and 3 cross-sectional area (CSA) measurements (Figure 7.1). Time-velocity waveform readings measured peak systolic velocity, mean diastolic velocity and time-average mean velocity (TAMV). TAMV measurements were calculated by the machine's software and represent the mean blood flow velocity for the duration of the waveform. CSA measurements were obtained on the B-mode transverse plane image. The mean of the three TAMV readings and three CSA readings were obtained at each scan in an attempt to increase reproducibility. SMA blood flow was then calculated using the

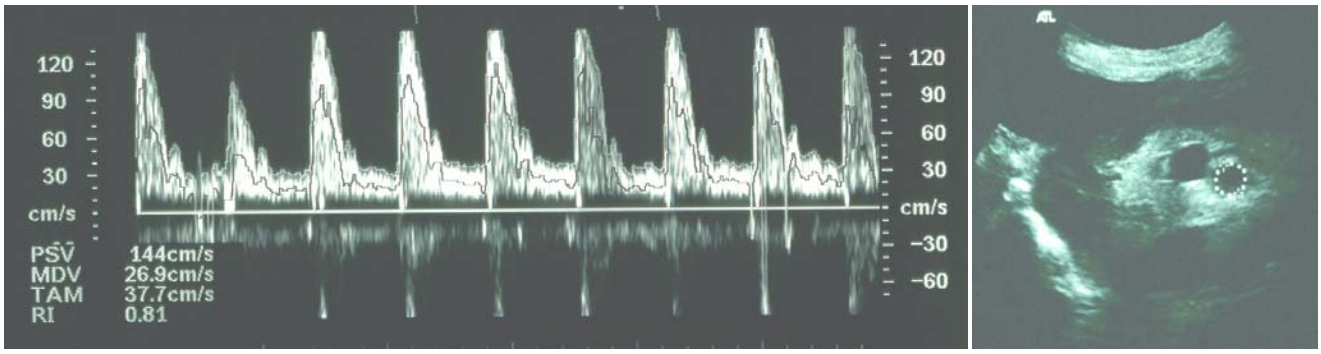


Figure 7.1: A time-velocity waveform reading (left) and a cross-sectional view of the SMA using B-mode imaging (dotted circle, right). SMA blood flow is a function of the mean TAMV and the mean CSA of the SMA. Readings from each patient were repeated three times at both the 9.00 am and 12.00 pm sittings to allow an average measurement to be calculated. Doppler and ultrasound images are reproduced with the consent of individual patients from this study.

formula:

SMA blood flow = Mean TAMV x Mean CSA

SMA flow on the postprandial scan was calculated in a similar fashion. Changes in flow were then quoted as a percentage of the preprandial flow. Preprandial flow was designated as 100%, such that an identical flow in subsequent postprandial assessments would be represented as 100% (i.e.: 100% of the original flow). This method avoided the documentation of negative flow changes which could otherwise wrongly suggest a change in the 'direction' of flow, as opposed to a simple diminution of perfusion.

7.2.2 Statistical analysis

Results were tabulated on an Excel® spreadsheet (Excel for Windows®, Microsoft Corporation, Redmond, Washington, USA) and then analysed using SPSS® for Windows® version 11.5 (SPSS®, Chicago, Illinois, USA). Results are presented as medians (IQR). Since there are numerous factors which may account for alterations in splanchnic flow, statistical comparisons were only made between the preprandial and postprandial SMA flow assessments of individuals within the same group, thus using individuals as their own controls. No attempt was made to quantitatively compare SMA

flows of patients in different cohorts. Only qualitative comparisons between groups were made. Relationships between measurements were assessed using Wilcoxon signed rank test for dependent variables and statistical significance was considered at the 5 percent level.

7.3 RESULTS

Of the 36 individuals recruited to the study, two were excluded as the SMA could not be identified on DUS. The 34 subjects comprised 14 healthy volunteers and 20 patients needing adjuvant nutrition. Of the 10 enterally fed patients, the reasons for feeding were as follows; 4 had failed a swallowing assessment but had an otherwise functioning gut, 3 were being ventilated while 3 patients required supplementation to meet nutritional requirements because of an inadequate oral intake. The 10 patients receiving TPN all had a non-functioning gastrointestinal tract (4 with prolonged ileus, 3 with high output fistulae, 2 had gastrointestinal obstruction and 1 had profuse diarrhoea). All 34 subjects tolerated their appropriate feeding regime well and had two SMA flow assessments at an interval of three hours as stipulated in the study protocol. Results for each group and other patient characteristics are summarised in Tables 7.3 and 7.4, as well as Figures 7.2 and 7.3.

The three volunteers in the CF group had a median SMA flow of 3.6 ml/s at 9 am and again 4.3 ml/s following a further 3 hour fast. There was no significant difference

Group	Number of patients	M:F ratio	Age (years)†	Pre vs. postprandial flow (ml/s)†	Median % flow change**	p-value
Controls, Fasting (CF)	3	1:2	28 (26 - 29)	3.6 (2.4 – 6.9) vs. 4. 3 (2.0 – 6.9)	119	**1.000**
Controls (CO), 600 kCal oral	6	3:3	30 (26 – 30)	7.6 (6.0 – 11.2) vs. 20.4 (16.9 – 27.9)	268	**0.046**
Controls (CE), NG (60ml/hr)	5	2:3	26 (25 – 28)	10.5 (7.8 – 12.4) vs. 16.0 (15.1 – 19.2)	152	**0.043**
Patients (PE), NG (60ml/hr)	10	5:5	73 (66 – 80)	7.3 (2.9 – 12.1) vs. 11.2 (8.2 – 25.0)	153	**0.007**
Patients (PT), TPN (125ml/hr)	10	3:7	82 (80 – 82)	14.5 (4.8 – 24.8) vs. 6.1 (2.4 – 9.2)	42	**0.013**
** Median postprandial flow as compared to median preprandial flow (assuming 100% represents no change)						

Table 7.3: Characteristics of the groups along with pre *versus* postprandial SMA measurements.

† Values are median (IQR); ** % change over a preprandial flow of 100%

Group	CF (n=3)	CO (n=6)	CE (n=5)	PE (n=10)	PT (n=10)
Age (years)	28 (26-29)	30 (26-30)	26 (25-28)	73 (66-80)	82 (80-82)
Sex (M:F)	1 : 2	3 : 3	2 : 3	5 : 5	3 : 7
Height (meters)	1.69 (1.66-1.71)	1.65 (1.63-1.67)	1.69 (1.65-1.74)	1.65 (1.62-1.73)	1.62 (1.57-1.66)
Weight (kg)	57 (54-60)	60 (56-64)	57 (53-62)	68.5 (65-74)	54 (46-65)
BMI	20.1 (19.6-20.6)	21.0 (20.5-22.3)	21.0 (20.0-21.0)	24.3 (22.5-28.4)	19.6 (17.5-23.0)
On ICU (%)	-	-	-	7 (70%)	8 (80%)
Postoperative (%)	-	-	-	6 (60)	5 (50)
MUST score	-	-	-	4 (3-4)	4 (3-5)
APACHE II	-	-	-	13 (10-17)	16 (12-21)

Table 7.4: Additional characteristics of the individuals in each group. MUST scores of $\geq$2 are indicative of a high risk for malnutrition. APACHE II scores were estimated prior to the fasting SMA assessment.
(BMI, body mass index; ICU, intensive care unit; MUST, malnutrition universal screening tool; APACHE, acute physiological and chronic health evaluation)

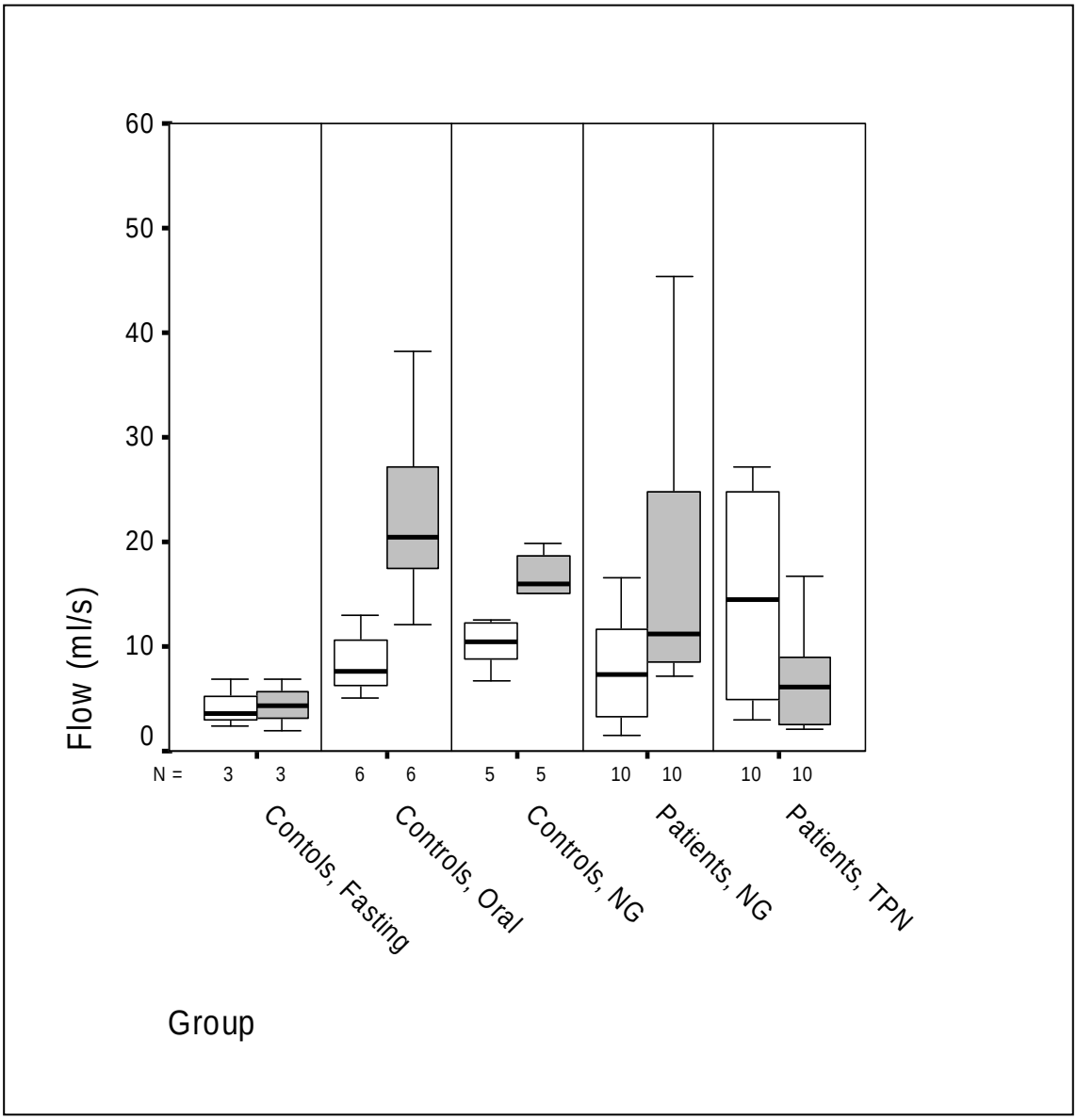


Figure 7.2: Box plots summarising the 9 o'clock (white) and 12 o'clock (grey) SMA flow measurements for each group.

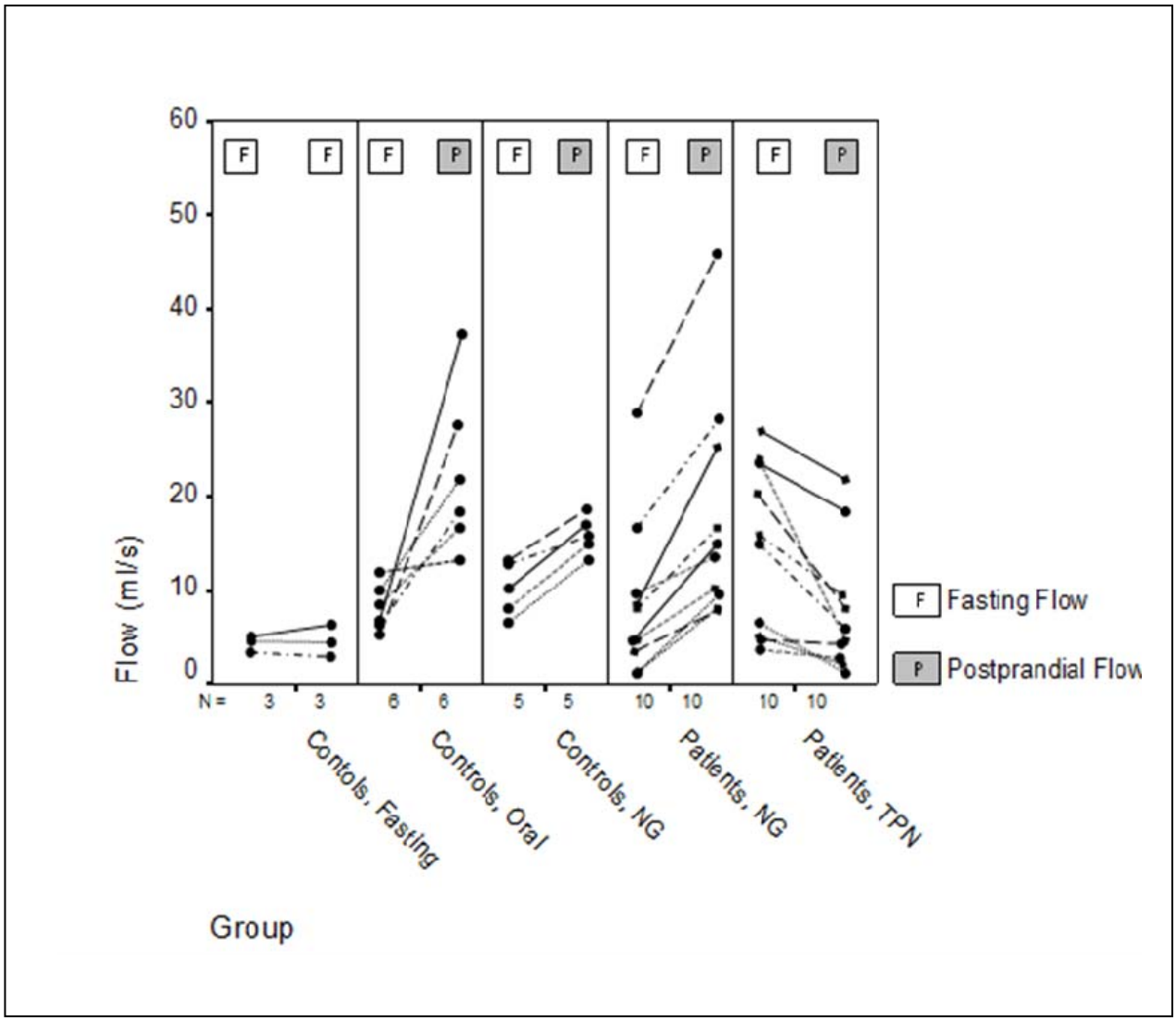


Figure 7.3: Before-and-after line plot demonstrates fasting and postprandial SMA blood flow assessments for each individual in the study. All patients fed orally or enterally experienced an increase in splanchnic flow after an enteral challenge. Conversly, all patients who recieved TPN demonstrated a drop in postprandial SMA flow when compared to their fasted state.

between the two assessments (p=1.000) suggesting reproducibility of this method of assessment. Controls administered an oral feed (CO group) had an increase in SMA flow from a median (IQR) of 7.6 (6.0 – 11.2) ml/s to 20.4 (16.9 – 29.9) ml/s postprandially (p=0.046). Following administration of a NG feed, volunteers in the CE group were also noted to have an increased SMA flow. This increased from a fasting flow of 10.5 (7.8 – 12.4) ml/s to 16.0 (12.1 – 19.2) ml/s postprandially (p=0.043).

Likewise, patients challenged with EN (PE group) also had a significant increase in SMA flow from 7.3 (2.9 – 12.1) ml/s up to 11.2 (8.2 – 26.0) ml/s (p=0.007) postprandially. All individuals fed orally or enterally (groups CO, CE and PE) demonstrated an increase in postprandial splanchnic perfusion when compared to fasting SMA blood flow estimations (Figure 7.3). Patients allocated to receive TPN (PT group) had a median fasting flow of 14.5 (4.8 – 24.8) ml/s which decreased significantly to 6.1 (2.4 – 9.2) ml/s (p=0.013) after feed administration. Each patient that was fed parenterally showed decreased postprandial SMA flows when compared to their preprandial measurements.

7.4 DISCUSSION: HOW FEEDING EFFECTS SPLANCHNIC PERFUSION

It is generally accepted that splanchnic blood flow increases following a meal, presumably as an adaptive response to facilitate digestion (Moneta *et al*., 1988). The results of this study corroborate with this and, in addition, demonstrate that PN causes a significant decrease in splanchnic perfusion in humans, as assessed by DUS. These fluxes

in alimentary tract blood flow may have implications to daily clinical practice particularly in the management of patients with a labile cardiovascular system, to those with suspected gut ischaemia, as well as to individuals at risk of gastrointestinal ischaemia-reperfusion injury (Ackland, Grocott and Mythen, 2000).

We recognise certain limitations with the design of this study. Firstly, the methodology employed describes a qualitative, not a quantitative assessment of pre- *versus* postprandial SMA blood flow. This was deemed appropriate because comparison between groups would have posed logistical problems because of the large number of variables that might impact on splanchnic flow. Age, height and weight, body surface area, rate of gastric emptying, and drugs, are some of the many factors thought to affect SMA flow, however the true effects of most of these factors on splanchnic perfusion remain poorly characterized in humans. To allow for these variables would require very large patient cohorts and prospective randomization into the various groups. It is not possible to randomize patients in studies such as this, as the decision as to whether patients require enteral or parenteral nutrition is a clinical one determined by underlying gut function and other considerations.

A second limitation is the fact that the study groups varied both with respect to the calorific value as well as the composition of the nutrients administered. It is well documented that different food constituents and changes in caloric load significantly affect splanchnic perfusion (Moneta *et al*., 1988; Parker *et al*., 1995). However, it must be reemphasised that the intention of the study was to make qualitative assessments of

SMA flow fluxes within groups, not absolute quantitative measurements or comparisons between disparate groups.

Thirdly, although assessments of SMA blood flow using DUS are well described, and despite being a non-invasive and reproducible method of measuring splanchnic blood flow, many would consider this method of measurement of blood flow suboptimal. It does not necessarily relate to end-organ perfusion, and as such its relevance to illness and patient management may be limited. Alternatives, which include vascular catheterization, dilution techniques, and surface mucosal transducers, have more appeal in these respects, but they tend to be more costly, increasingly labour-intensive, dependent on specialised equipment and comparatively more invasive, subjecting patients to risks of both complications as well as radiation. Their reproducibility and specificity has also been questioned (Apostolakos, 1995; Ackland, Grocott and Mythen, 2000). Notwithstanding these limitations we feel the trends observed within groups in this study are probably correct.

The gastrointestinal tract is central to the pathogenesis of many disease states and is thought to be the motor which drives MOF (Marshall, Christou and Meakins, 1993; Nieuwenhuijzen, Deitch and Goris, 1996; MacFie, 2000; Ding and Li, 2003). The mechanism by which this occurs is thought to relate to a breakdown in gut barrier function possibly mediated or propagated by BT (MacFie, 2000; Magnotti and Deitch, 2005; Deitch, Xu and Kaise, 2006). It has been suggested that a predisposing factor to translocation is ischaemia-reperfusion injury to the gut, which is likely to be significantly

influenced by splanchnic flow (Deitch, Xu and Kaise, 2006). Clearly therefore, any intervention that impacts on splanchnic flow is potentially significant, particularly in the critically ill patient.

One such intervention is the role of adjuvant feeding in hypovolaemic or otherwise haemodynamically labile patients. Blood is normally diverted away from the splanchnic circulation to more 'vital' organs in states of shock or critical illness. The institution of early enteral feeding and resultant gastrointestinal hyperaemia may potentially upset this protective homeostatic function, particularly in critically ill patients where early adjuvant feeding is routinely advocated (Dominioni *et al*., 2003; Artinian, Krayem and DiGiovine, 2006). There are isolated reports of gut ischaemia occurring in patients following instigation of EN and it is possible that alterations in splanchnic flow occurring as a consequence of nutritional support are responsible (Lawlor, Inculet and Malthaner, 1998; Jorba *et al*., 2000; Munshi, Steingrub and Wolpert, 2000).

There are no published studies which have investigated the effects of variations in SMA flow with TPN in humans. Our results suggest that TPN is associated with a significant reduction in SMA flow. We consider it unlikely that this is a type 1 statistical error on the basis that it occurred in all patients and the changes observed were significant. In addition a study by Niinikoski *et al.* (2004) using the piglet model corroborates this finding of TPN-associated decrease in SMA blood flow. The mechanisms which bring about these changes in perfusion remain unclear. It is the authors' opinion that either it has to occur as a consequence of a systemic effect or as a result of redistribution of blood flow within

the splanchnic circulation. Definitive conclusions in this respect cannot be drawn from the results of this study as changes in systemic blood flow were not directly assessed; however the author considers a systemic effect unlikely. All patients in the study were systemically stable and were closely monitored throughout the study. Further, any systemic effect of TPN would be likely to increase cardiac output as a consequence of increased metabolic rate and increased stroke volume. It is well known that intravenous infusion of substrates such as glucose or amino acids results in an increase in metabolic rate particularly if infused in excess of requirements (Carlson *et al*., 1994; Brundin, Branstrom and Wahren, 1996; Sellden, 2002). Recruited patients were systemically stable and the volumes of TPN administered are not such that one would anticipate significant effects on metabolic expenditure. The alternative explanation relates to redistribution of blood flow. In particular, the possibility that intravenous infusion of nutrients causes an increase in portal, hepatic and systemic perfusion with a commensurate reduction in SMA flow. We know of no human or animal data to corroborate this hypothesis with TPN, but it is interesting to note that Brudin *et al.* reported that intravenous glucose administration resulted in increased metabolism (as evidenced by increased oxygen demands and thermic effect) and blood flow in extrasplanchnic tissue, with a corresponding, albeit lesser, decrease in splanchnic expenditure and perfusion (Brundin, Branstrom and Wahren, 1996). In other words, intravenous caloric loads appear to increase overall basal metabolism while preferentially shunting blood to other tissues and away from the gut, and is consistent with our own observations in the present trial.

The constituents and volume of feeds administered to the gut as well as the site of enteral delivery appear to differentially influence fluxes in SMA flow. In a small study of 6 volunteers, Parker *et al.* (1995) elegantly demonstrated that postprandial SMA flow increases correlated positively with the energy content of an oral meal (r=0.969) possibly by influencing gut hormone release, in particular N-terminal neurotensin (r=0.967) and plasma noradrenaline (r=0.900). Using DUS, Moneta *et al.* (1988) were able to detect changes in SMA, but not coeliac or femoral artery blood flow following the administration of enteral meals of varying protein, fat and carbohydrate compositions. Further, Meehan and Kreulen (1992) report that large intestinal distension leads to SMA smooth muscle hyperpolarization and a resultant increased blood flow in an animal model, while Geelkerken and co-workers (1998) were able to demonstrate that the site of meal stimulation within the gut also effected gastrointestinal blood flow. While quantitative comparisons between groups were not possible in the present study, qualitative differences demonstrate that the intravenous delivery of nutrients represents yet another factor which influences SMA blood flow and highlights a poor understanding of factors which modulate gastrointestinal perfusion.

7.5 CONCLUSION

In conclusion, it is widely accepted that an increase in SMA flow is a normal physiological adaptive response to an increase in oxygen demand associated with oral and enteral intakes. To date, it is not yet possible to discriminate between the supportive

and stressful effects of enteral feeding (Brundin, Branstrom and Wahren, 1996; Trager *et al*., 2001) nor, similarly, the adaptive or ischaemic effects brought about by TPN-induced decreased SMA perfusion. Much remains to be established about changes to splanchnic flow in humans. Future studies investigating patient characteristics and other extrinsic factors which modulate splanchnic flow are much needed, as are trials investigating the mechanisms involved. The results of this study confirm increases in SMA flow in individuals receiving oral or EN. However, the most striking observation was a significant decrease in splanchnic flow in every patient receiving TPN. The clinical significance of these findings requires further investigation.

CHAPTER 8:

MODULATION OF INTESTINAL FUNCTION USING GUT–SPECIFIC NUTRIENTS AND ITS EFFECTS ON OUTCOME

'A state without the means of some change
is without the means of its conservation.'

Edmund Burke
Irish Statesman, 1729 -1797

8.1 INTRODUCTION: WHAT ARE GUT-SPECIFIC NUTRIENTS?

Intolerance to an enteral diet is common, particularly in postoperative surgical and critically ill patients and has been independently associated with prognosis (chapters 4 & 5). As a result, enhancing the recovery of gut function or curtailing the period of gut failure may be associated with corresponding improvements in patient outcomes.

Numerous therapeutic interventions, such as prokinetics, epidural or spinal anaesthesia, postpyloric delivery or alterations to feeding protocol have been investigated as means of enhancing enteral tolerance, possibly by modulating gut function. These and other therapies assume that gut function can be modulated in the first place, and their implementation has had varying degrees of success on the return of gut function (Kehlet, 2000; Mentec *et al*., 2001; Kehlet and Holte, 2001; Davis *et al*., 2002; Binnekade *et al*., 2005; Gatt *et al*., 2005; Traut *et al*., 2008).

The use of GSN represents a novel means of enhancing the return of gut function as assessed by enteral tolerance. While an extensive literature exists on their usage, no previous study has selected a 'cocktail' of these nutrients and used them in a prospective study in which the primary end point was return of gut function. As such, the primary aim of this study was to record the effects of a cocktail of GSN on the time to return of normal gut function in critically ill patients. For purposes of this study normal gut function was defined by the oral or enteral tolerance of 80 per cent or more of calculated nutritional requirements over a minimum consecutive period of 48 hours.

8.2 METHODS

This study was approved by the Scarborough LREC (Ref. No. LREC/04/378). Critically ill patients considered to have gut failure by the Scarborough Hospital multidisciplinary nutrition team were eligible for recruitment. For the purposes of this trial, critical illness was defined by the failure of at least one organ system without necessarily requiring admission to the intensive care (ICU) or high dependency units (HDU).

On entry into the study, all patients were receiving PN by virtue of their gut failure. Exclusion criteria included the failure to obtain consent (or assent by the next-of-kin), known intolerance to one or more of the study preparations (Table 8.1), age <18yrs, and pregnancy. Patients who were strictly 'nil-by-mouth' and therefore unable to receive the study preparations or appropriate placebos were also excluded.

The basic study design was that of a double-blind, externally randomized, placebo-controlled clinical trial. The study design is summarised in a flow diagram in Figure 8.1. Subject to informed consent (or assent from the next-of-kin in case of ventilated/sedated patients), patients were randomized to one of two study arms, either a control group (receiving placebo) or a study group (receiving GSN). For purposes of blinding the placebos were visually indistinguishable from the GSN preparations. All preparations were administered for one month and patients were followed up for a total of 3 months or until death.

GSN cocktail	Placebo cocktail
1. **Multivitamin Capsules:** Forceval® Alliance Pharmaceuticals**,** Chippenham, UK (Formerly provided by Unigreg Ltd) **Dose**: 1 capsule daily. **Route:** Oral/via NGT dissolved in milk	1. **Multivitamin Placebo Capsules:** Forceval® placebo, Alliance Pharmaceuticals**,** Chippenham, UK (Formerly provided by Unigreg Ltd) **Dose**: 1 capsule daily. **Route:** Oral/via NGT dissolved in milk
2. **Probiotic Capsules:** Trevis® Chr. Hansen, Hørsholm, Denmark **Dose**: 1 capsule three times a day. **Route:** Oral/via NGT dissolved in water	**2. Probiotic Placebo Capsules:** Trevis® placebo, Chr. Hansen, Hørsholm, Denmark **Dose**: 1 capsule three times a day. **Route:** Oral/via NGT dissolved in water
3. **Prebiotic Powder:** Oligofructose Orafti, Tienen, Belgium **Dose**: 16g/day in 2 divided doses **Route:** Oral/via NGT dissolved in water	3. **Prebiotic Placebo Powder:** Ground sucrose **Dose**: Twice daily administration **Route:** Oral/via NGT dissolved in water
4. **Glutamine: (**2 options) Dipeptiven® Fresenius Kabi, Bod Homburg, Germany **Dose**: 100ml dly **Route:** Intravenous or GlutaminOx® 5g powder sachets Oxford Nutrition, Witney, UK **Dose**: 20 g/day in four divided doses / day **Route:** Oral/via NGT in 4x200ml water	4. **Glutamine Placebo: (**2 options) Sterile saline for iv administration **Dose**: 100ml dly **Route:** Intravenous or Ground sucrose **Dose**: Four divided doses / day **Route:** Oral/via NGT in 4x200ml water

Table 8.1: Preparations administered to the two arms of the study

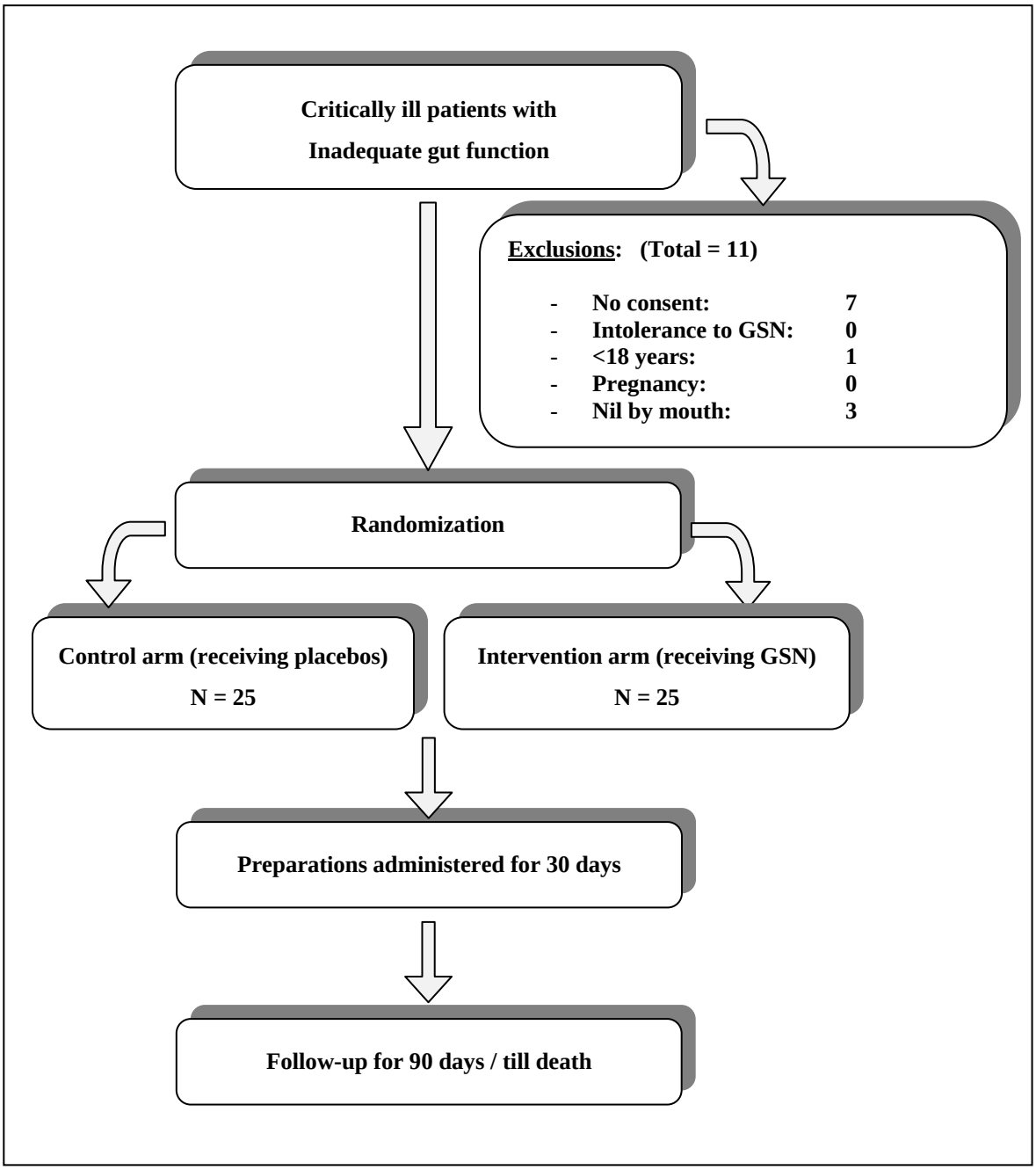


Figure 8.1: Flow diagram of study design

The cocktail of GSN comprised a combination of a prebiotics (oligofructose, Orafti, Tienen, Belgium), a multi-strain probiotics (Trevis®, Chisten Hansen, Hørsholm, Denmark), a multivitamin/antioxidant preparation (Forceval®, Alliance Pharmaceuticals**,** Chippenham, UK; formerly provided by Unigreg Ltd.) and glutamine (GlutaminOx®, Oxford Nutrition, Witney, UK or Dipeptiven®, Fresenius Kabi, Bod Homburg, Germany) the details of which are shown in Table 8.1. Each capsule of Trevis® contained $4x10^9$ colony forming units of *Lactobacillus acidophilus La5*, *Lactobacillus bulgaricus*, *Bifidobacterium lactis Bd-12* and *Streptococcus thermophilus*. The constituents of Forceval® are summarised in appendix 5. Glutamine (or its placebo) was administered intravenously for the first 7 days and then orally or enterally thereafter. All other preparations were administered orally or dissolved in small quantities of fluid and administered via an indwelling nasogastric tube (NGT) from recruitment. Patients in both groups received appropriate supplementation of physiological doses of essential macro- and micro-nutrients, so that any GSN provided to the intervention arm where over and above physiological requirements.

All nutritional support was managed by a multidisciplinary hospital nutrition team. Nutritional support is usually entertained in patients with an anticipated or actual inadequate oral intake of five days duration or more, with or without the evidence of malnutrition, risk of malnutrition (as predicted by the malnutrition universal screening tool [MUST] Todorovic *et al*., 2003) and/or the presence of critical illness. The quantity and method of feeding was based on individually calculated nutritional requirements using the modified Schofield equation (Todorovic and Micklewright, 2004) and aimed to

provide intakes of 20 – 25 kcal kg^{-1} d^{-1} non-protein energy and approximately 0.17g nitrogen kg^{-1} d^{-1}. Nutritional requirements were calculated by senior dieticians, and feed administration was guided by strict feeding protocols along the principles of optimal nutritional support to ensure a more adequate delivery of both macro- and micronutrients. EN was provided using Fresubin Original® 1 kcal ml^{-1} polymeric feed (Fresenius Kabi Ltd, Cheshire, United Kingdom), and PN was administered using Kabiven® 9 or 14 depending upon requirements (Fresenius Kabi Ltd, Cheshire, United Kingdom). The constituents of these commercially available feed preparations is summarised in appendix 5. GSN provided to the intervention arm where in addition to basal requirements.

8.2.1 End points recorded

The primary end point of this study was the time to the return of normal gut function. This was calculated in hours from the commencement of the study preparations to the oral/enteral tolerance of $\geq$80% of calculated nutritional requirements for a minimum continuous period of 48 hours (Gatt *et al*., 2007). The state of gut function was also evaluated daily by the traditional assessments of bowel sounds, passage of flatus, passage of faeces/diarrhoea, bloating, abdominal distension, high NG aspirates, vomiting and feed aspiration. Episodes of feed intolerance were determined by documented episodes of vomiting, feed aspiration, severe abdominal pain, distension or bloating that necessitated cessation or alterations to feed administration as guided by the unit's feeding protocols. The use of opiates, overall fluid balance, as well as the need for surgery, were recorded as

predisposing factors for ileus. The duration of intravenous infusions was recorded as a surrogate indicator of fluid tolerance by the gut. IP was also assessed on entry into the study and on days 30 and 90 by employing the triple sugar test of lactulose, rhamnose and sucralose is described in section 2.4.1. A log was kept of all analgesic requirements, and particularly the use of opiates which are known to effect gut function. Similarly, the use of prokinetic medications including metoclopramide and erythromycin, and the amount of GSN administered to each patient was also registered.

Multiple other end points were recorded. These are summarised in Table 8.2 together with the periodicity of the measurements taken. Patients were reviewed at least twice daily for the duration of their hospital stay, and then at one month and again at three months from recruitment. Data were all collected prospectively. In view of the multiple end-points recorded, emphasis in the results section below will be given to those which showed significant differences between groups.

APACHE II scores were calculated on admission into the study, weekly thereafter for the duration of hospital stay, and again on days 30 and 90. Details of organ failure were recorded including the duration of support with inotropes, ventilators and/or dialysis. The occurrence of septic, non-septic, and feed related complications were recorded for the duration of hospital stay. Septic complications were defined as the presence of recognised pathogens in normally sterile body tissues, confirmed by culture and supported by clinical, haematological and/or radiological evidence.

Variables			
Demographics	**Nutritional data**	**Other organ failures**	**Complications & clinical outcome**
Age *	Weight ‡	Cardiac §	Septic §
Sex *	Weight prior to illness *	Respiratory §	Tube related §
Height *	Weight change ‡	Renal §	Feed related §
	BMI ‡	Hepatic §	
Hospital stay	Nutritional requirements §	Neurological §	**Lab/X-ray investigations**
Length of hospital stay	Reason for feeding *	Haematological §	Chest and abdominal X-rays *
Need for ICU admission §	Length of feeding		Full blood count ‡
Length of ICU admission	<5 days feeding	**Severity of illness**	Urea, creatinine & electrolytes ‡
Diagnosis *	Length of TPN	ASA score *	Liver function tests & albumin ‡
Need for hospital readmission ᶠ	Length of EN	APACHE II score ‡	Zinc, phosphate, magnesium ‡
Total length of stay	Need for combination feeding §	SIRS / Sepsis syndrome §	CRP ‡
	Method of feed administration §	Need for ventilation §	
Operative data	Volume of feed prescribed §	Length of ventilation	**Fluids & fluid balance**
Surgery during admission §	Volume of feed administered §	Need for inotropic support §	Fluid balance §
Operation performed §	Cumulative energy balance	Length of inotropic support	Time to discontinuation of IVI
Date/s of operation §	Weekly energy surplus/deficit ‡	Need for dialysis §	
Presence of a stoma §	Reasons for inadequate intake §	Length of dialysis	**Psychological wellbeing**
		Duration of catheterization	HAD score ᚼ
Intestinal permeability (triple sugar)	**Nutritional status & anthropometry**		
Urinary lactose:rhamnose ratio ᚼ	MUST *	**GSN / Placebo**	**Pain & fatigue assessments**
Urinary sucralose excretion ᚼ	Serum albumin ‡	Amount administered §	Visual analog scales ‡
	Mid-arm circumference ‡	Adverse reactions §	
Gut function	Skin fold thickness ‡	Palatability of preparations ᶠ	**GP visits after discharge** ᶠ
Clinical assessment §			
Tolerance to oral/enteral intake §	**Strength & mobility**	**Drugs** §	**Mortality data**
Episodes of intolerance §	Grip strength ‡	Analgesics/opiates/epidural	Death in first 3 months
Reasons for intolerance §	Spirometry ‡	Antibiotics	Date of death
Time to return of gut function ᚼ	Time to mobilization §	Prokinetics	Time to death from recruitment
	Time to activities of daily living §	Other medications	Cause of death

Table 8.2: Variables recorded. The primary outcome was the time to the return of normal gut function. (Periodicity of measurements: * on recruitment only, § daily during admission, and on days 30 & 90 where applicable; ‡ weekly during admission and on days 30 & 90 where applicable; ¥ on discharge; ᶠ after discharge or on days 30 & 90 only; ᚼ see text)

A number of anthropometric parameters and other indicators of physiological and psychological well-being were also recorded. FEV_1 and FVC were recorded using a portable spirometer (Vitalograph® Limited, Buckingham, UK). MAC, skin fold thickness and hand grip strength were recorded on the non-dominant side. Skin fold thickness was assessed using an apposite digital skin fold measuring calliper (Oxford Nutrition, Witney, UK). Hand grip strength was measured using a Jamar® dynamometer (NexGen Ergonomics, Montreal, Quebec, Canada). Strict charting of all input and output was maintained to calculate overall fluid balance. Mobilisation was recorded daily, assisted by the use of a patient diary of daily activities. The time spent by the patient out of bed on each day, the time to mobilise to the toilet with help and unaided, and the time to walk the length of the ward with help and independently were all recorded for comparison.

Patients had daily clinical observations and regular blood investigations carried out as part of their in-hospital care. Serum albumin, white cell count estimates and CRP were also recorded as indicators of the acute phase response. Ten centimeter visual analogue scales without intersections were used to record fatigue and pain scores on a weekly basis. Pain assessments were performed at rest, on coughing and on movement. Cognitive function was determined by means of a validated hospital anxiety and depression (HAD) questionnaire summarised in appendix 3 (Zigmond and Snaith, 1983).

The length of hospital and ICU stay (where relevant) were recorded. Following discharge, the need for patient readmission and the total number of GP (GP) visits were

documented at one and three months. Details of mortality were recorded for 3 months after hospital discharge.

8.2.2 Randomization and blinding

All members of staff and patients were blinded to treatment allocation. This was aided by the availability of visually identical study and placebo preparations. Randomization was performed externally by telephone. The individual involved was independent of the research team. For purposes of patient allocation, reference was made to lists of randomly generated numbers with no fixed starting point which ensured a 1:1 allocation to groups. A coding system then permitted the appropriate dispensation of products by the pharmacy department without compromising the blinding process. The randomization sequence was only deciphered once all patients had completed the 3 month follow-up period.

8.2.3 Statistics and sample size calculation

Results were tabulated on an Excel® spreadsheet (Excel for Windows®, Microsoft Corporation, Redmond, Washington, USA) and then analysed using SPSS® for Windows® version 11.5 (SPSS®, Chicago, Illinois, USA). Results for non-parametric data were expressed as medians (IQR). Relationships between groups were assessed using χ^2

test for binary outcomes or Fischer's exact test for small cohorts as appropriate. Continuous variables were compared with the Mann-Whitney *U*-test. Changes over time within groups were analysed with Friedman's test. Statistical significance was considered at the 5 percent level.

No similar study could be identified in the literature for purposes of a power calculation. For this reason, sample size was estimated from a previous study performed by the author and described in chapter 5 (Gatt *et al*., 2007). In this earlier study the median time to the return of normal gut function was 141 hours from commencement of the study, with a mean of 191 hours. A power calculation showed that a minimum of 21 patients would be required in each arm in order to demonstrate a difference in return of gut function of 72 hours at the 5% level of significance with a power of 90%. Correcting for the 16% of patients in this previous study that never achieved normal gut function would require an additional 4 patients per cohort, resulting in a total of 25 patients per arm.

8.3 RESULTS: EFFECTS OF GSN ON GUT FUNCTION

A total of 50 patients were recruited to the trial, with 25 randomized to each of the two arms of the study. The two groups were similar in all respects as summarised in Table 8.3. This included disease severity as assessed by APACHE II scoring, prevalence of surgery as well as opiate and prokinetic usage.

Factor	Control arm (Placebos) N=25	Intervention arm (GSN) N=25	P-value*
Demographics			
Age (years) *	73.4 (65.4–80.4)	63.3 (56.2–76.4)	0.308
Sex			0.191
Male	11	16	
Female	14	8	
Hospital Stay			
Needing surgery (%)	15 (60)	13 (52)	0.569
Admitted to ICU (%)	12 (48)	16 (64)	0.254
Nutritional parameters			
Height (meters) *	1.71 (1.54-1.80)	1.78 (1.62-1.88)	0.343
Weight (kg) *	73.6 (61.0-94.6)	77.6 (62.3-98.7)	0.157
BMI *	24.2 (19.1-32.2)	24.6 (18.4-31.0)	0.778
Nutritional requirements (kcal/day) *	1520 (1424–1650)	1610 (1455–1875)	0.388
MUST score *	3 (2-3)	3 (2-3)	0.945
Severity of illness			
ASA grade *	3 (2–3)	3 (3–3)	0.883
Initial APACHE II score *	10 (9–15)	11 (8–14)	0.404

Table 8.3: Basic characteristics of both groups. Cohorts were comparable in all respects. (* figures represent median (IQR) values)

The administration of GSN resulted in a significantly earlier return of normal gut function when compared to controls (respectively 164 (120–225) hours *versus* 214 (184–401) hours; p=0.016) as illustrated in Figure 8.2. This is despite patients in both groups being started on an oral/enteral diet at comparable times from recruitment (respectively 52 (12–136) hours *versus* 69 (44–151) hours; p=0.201). No differences in fluid balance, opiate usage, prokinetic drug administration or abdominal surgery could be detected between groups during this time period.

This earlier return of gut function in the GSN group was not associated with any detectable differences in anthropometric, physiological or psychological parameters (Table 8.4). In addition, no difference were detected between the two groups in small gut (5 hour L:R ratios), whole gut (24 hour sucralose excretion) or colonic (final 19 hour sucralose excretion) permeability at any time point when measurements were taken (Table 8.4). In addition, there was no change in permeability measurements over the study period that could be detected within groups using Friedman's test (results not shown).

There were no detectible differences in the acute phase response between the groups at any single time point as measured by white cell count, CRP and serum albumin assessments (Figure 8.3). However, when changes over time within groups were assessed using Friedman's test, the patients receiving GSN were noted to have a significant increase in serum albumin with time (p=0.048). Increases in absolute serum albumin levels were also noted in the control group, but these did not achieve significance

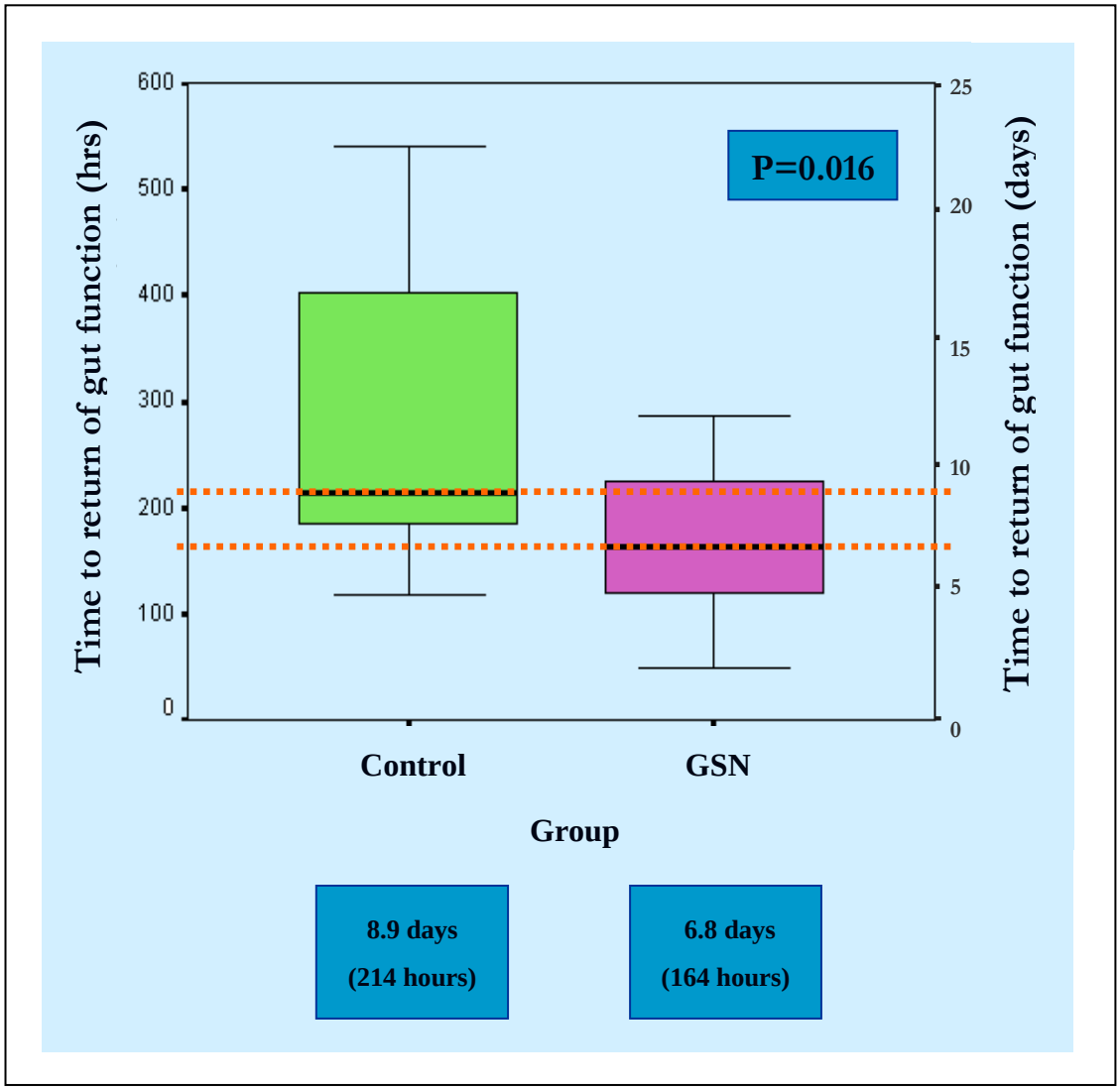


Figure 8.2: Time to return of normal gut function for the two groups. Time is shown in both hours (left y-axis) and days (right y-axis). The administration of GSN resulted in a significantly earlier return of normal gut function when compared to controls receiving placebos (p=0.016). Medians for the two groups are highlighted by the two dotted lines.

Factor	Control arm (Placebos)	Intervention arm (GSN)	P-value*
Patients tolerating placebos/GSN (%)	25 (100)	25 (100)	1.000
Nutritional parameters			
Length of feeding (hours) *	122 (77–231)	121 (98–208)	0.891
Time to starting oral intake (hours) *	69 (44–151)	52 (12–136)	0.201
Time to tolerance (hours) *	214 (184–401)	164 (120–225)	**0.016**
Patients receiving prokinetics (%)	23 (92)	23 (92)	1.000
Organ Failure			
Cardiac Failure (%)	4 (16)	2 (8)	0.864 **
Respiratory failure (%)	5 (20)	6 (24)	0.432 **
Renal failure (%)	2 (8)	1 (4)	0.824 **
Hepatic failure (%)	2 (8)	1 (4)	0.824 **
Neurological failure (%)	0 (0)	2 (8)	0.965 **
Haematological failure (%)	1 (4)	0 (0)	0.942 **
Intestinal permeability			
Day 0 L:R (small gut) *	0.125 (0.070–0.227)	0.055 (0.029–0.097)	0.057
Day 0 Sucralose (whole gut) *	0.795 (0.225-3.539)	0.715 (0.155-1.975)	0.704
Day 0 Colonic (19 h sucralose) *	0.372 (0.009-1.445)	0.205 (0.103-0.530)	0.255
Day 90 L:R (small gut) *	0.074 (0.038-0.113)	0.042 (0.023-0.068)	0.463
Day 90 Sucralose (whole gut) *	0.260 (0.180-1.780)	0.570 (0.090-1.450)	0.739
Day 90 Colonic (19 h sucralose) *	0.164 (0.142-1.640)	0.270 (0.001-0.680)	0.641

Factor	Control arm (Placebos)	Intervention arm (GSN)	P-value*
Complications			
Any	18 (72)	10 (40)	**0.227**
Septic	13 (52%)	4 (8%)	**0.015 ****
Feed related	6 (24%)	4 (16%)	0.725 **
Delivery system related	7 (28%)	4 (16%)	0.496 **
Hospital Stay			
Length of hospital stay (days) *	29 (17–43)	24 (15–42)	0.691
Number of readmissions *	1 (0-1)	0 (0-1)	0.342
Total length of stay (days) *	37 (19–51)	31 (15–44)	0.516
GP visits after discharge *	1 (0-1)	0 (0-1)	0.331
Mortality			
Death by 90 days (%)	7 (28%)	2 (8%)	0.138
Time to death (days) *	29 (5–51)	56 (30–101)	0.494

Table 8.4: Physiological parameters and other end points recorded for the two groups. (* figures represent median (IQR) values)

(p=0.054). Both groups showed a significant decrease in CRP over time, (respectively p<0.001, and p<0.001) but no change in their WCC (respectively p=0.144, and p=0.227). These changes over time are represented diagrammatically in Figure 8.3.

A total of 17 (34%) patients developed 20 culture-proven septic complications during the study period. Thirteen (52%) of these patients (15 septic episodes) were randomized to the control arm while the remaining 4 (16%) patients (5 septic episodes) received GSN (p=0.015). Figure 8.4 summarises the twenty septic complications detected.

There were no recordable differences between the two groups with regards to the presence of other single organ failures, the time patients required organ support with inotropes, ventilators or dialysis and the length of ICU stay. In addition, initial hospital stay, the number of readmissions and total hospital stay (to include readmissions) was similar for both groups, as were the total number of GP visits after discharge. There were a total of 9 deaths which occurred during the 3 month study period. Seven (28% of all patients in the group) of these occurred in patients in the control arm with 2 (8% of all patients in the group) occurring in patients receiving GSN during the same time period (p=0.138). Causes of death are summarised in Figure 8.5. Four (8%) patients had persistent gut failure for the duration of the study period. Three (12%) of these were randomized to the control group, and 1 (4%) was receiving GSN (p=0.609). All 4 patients who had persistent gut failure died during follow-up.

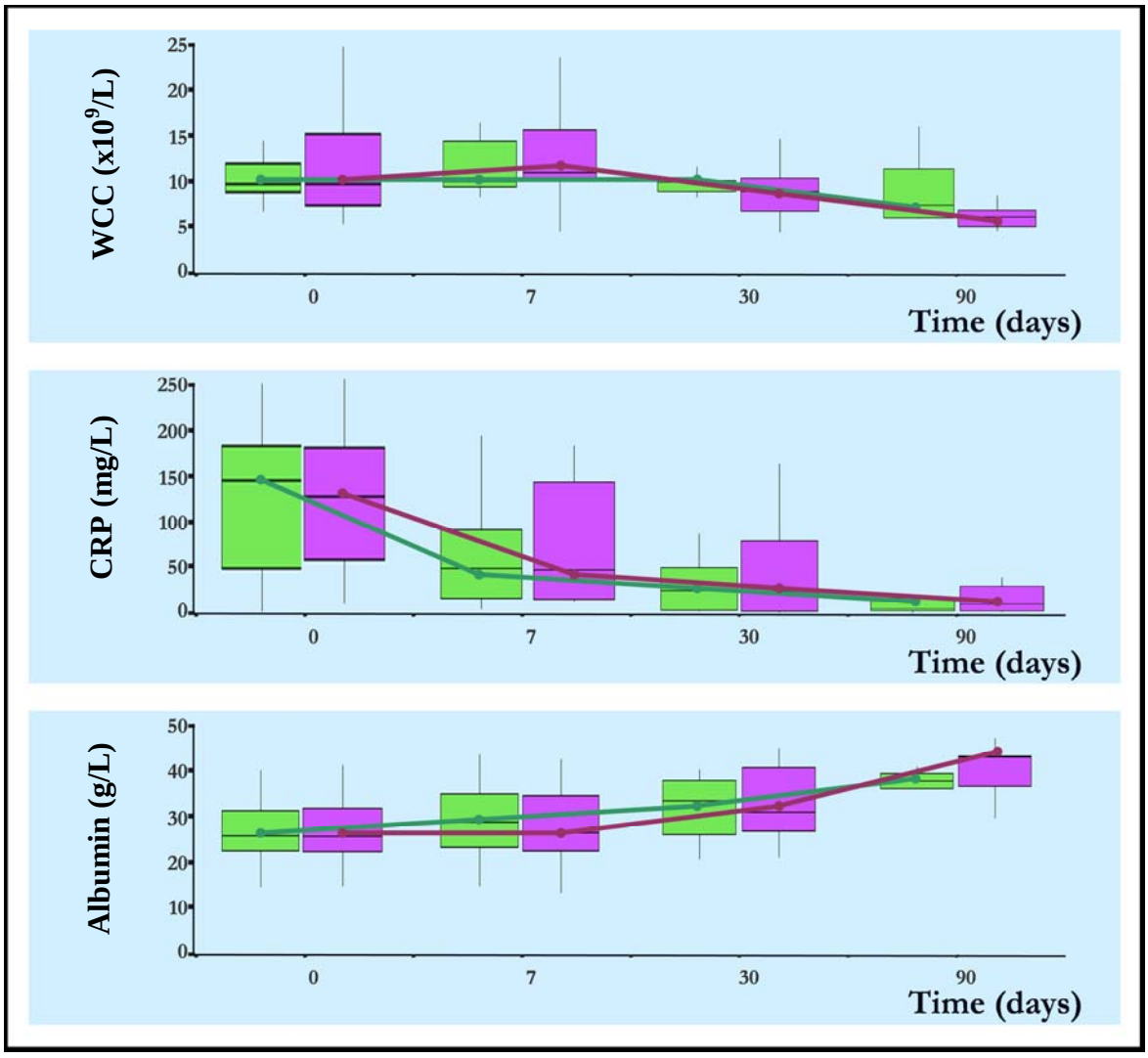
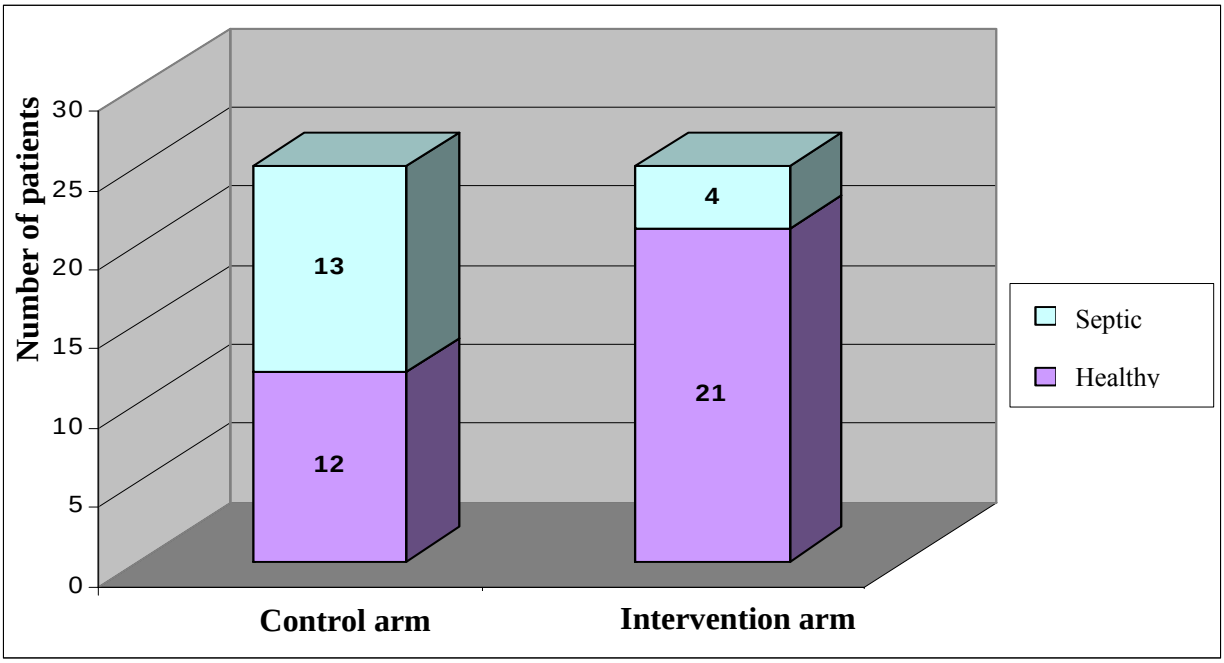
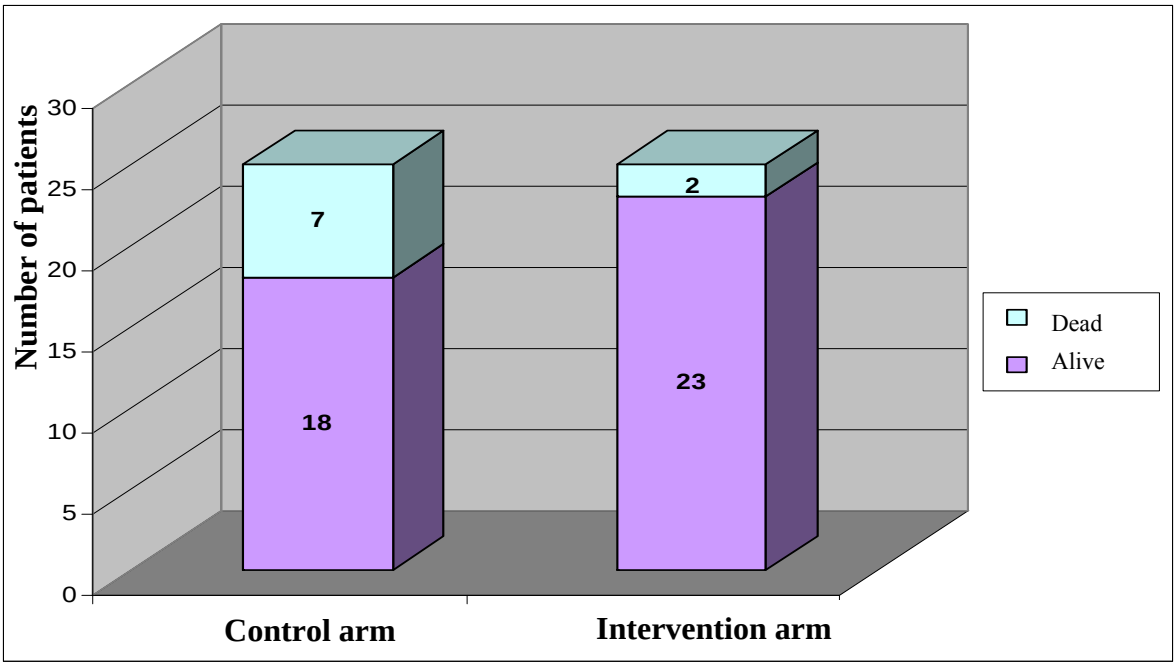


Figure 8.3: Changes in the acute phase response with time. Controls are represented in green and patients receiving GSN in purple. There were no differences between the groups at any time point. Changes over time within groups were assessed using Friedman's test. There was no change in WCC over time in either group ($p=0.227$ *vs.* $p=0.144$ respectively). CRP estimates decreased with time in both arms ($p<0.001$ *vs.* $p<0.001$ respectively). Both groups showed increases in serum albumin with time, but this was only significant in the GSN group ($p=0.048$ *vs.* $p=0.054$ respectively).



Septic complications	Control arm (Placebos) N=25	Intervention arm (GSN) N=25
Abdominal collection	5	-
Chest infection	2	2
Wound infection	2	1
Clostridium difficile colitis	2	-
Line sepsis	2	1
Bacteraemia / Sepsis	1	1
UTI	1	-
Total	15	5

Figure 8.4: The number of patients in each group who developed septic complications (13 vs. 4) and a list of the 20 culture-proven septic episodes.



Septic complications	Control arm (Placebos) N=25	Intervention arm (GSN) N=25
Septic shock / MOF	3	1
Severe pancreatitis	1	1
Pneumonia	1	-
Renal failure	1	-
Liver failure	1	-
Total	7	2

Figure 8.5: Summary of patient mortality in both groups and the causes of death.

8.4 DISCUSSION: EFFECTS OF GSN ON GUT FUNCTION

The results of this study demonstrate that the provision of GSN to critically ill patients with non-functioning gastrointestinal tracts was associated with an earlier return of gut function as assessed by enteral tolerance. GSN administration was also associated with an attenuation of the acute phase response, a decrease in the number of septic episodes, and a reduction in the absolute number of deaths (albeit non-significant). The implication from these results is that similar to the function of other single organs, gut function can also be modulated and this is associated with measurable improvements in outcome.

There is increasing recognition of the importance of the 'gut barrier' in health and disease. Failure of the gut barrier has been associated with significant increases in both morbidity and mortality (O'Boyle *et al*., 1998). The primary interface between ingested nutrients and the blood and lymphatic systems and an integral part of the gut barrier are the gastrointestinal epithelial cells. These epithelial cells are dependent on both luminal and bloodstream sources for nutrition. Certain nutrients, collectively known as gut-specific nutrients (GSN), have been shown to exert specific effects on these epithelial cells and hence on intestinal mucosal integrity (Duggan, Gannon and Walker, 2002). Additionally, GSN have important effects on gastrointestinal function and gut immunology, which are separate and distinct to their role as nutrients or immunomodulators.

Numerous substances have been shown to have 'gut-specific' effects and include

glutamine (Burke *et al*., 1989; O'Dwyer *et al*., 1989; Van der Hulst *et al*., 1993; Tremel *et al*., 1994; Heyland *et al*., 2001[b]; Wischmeyer, 2005; Wischmeyer, 2007), arginine (Daly, Reynolds and Thom, 1988; Daly *et al*., 1992; Bowler *et al*., 1995; Alican and Kubes, 1996; Schleiffer and Raul, 1996; Senkal *et al*., 1995; Weimann *et al*., 1998; Luiking and Deutz, 2007; Vermeulen, 2007), zinc (Koo and Turk, 1977; Clarkson and Elmes, 1987; Roy, 1992; Wapnir, 2000), vitamin A (McCullough, Northrop-Clewes and Thurnham, 1999; Thurnham *et al*., 2000), probiotics (Bengmark, 1996; Sanders, 2000; Lu and Walker, 2001), prebiotics (Gibson *et al*., 1995; Niness, 1999), short-chain fatty acids (Daly *et al*., 1992; Weimann *et al*., 1998; Teitelbaum and Walker, 2001), and nucleotides (Daly *et al*., 1992; Weimann *et al*., 1998; Carver, 1999). However, despite the fact that enormous research endeavour has been undertaken investigating these substances, their role in clinical practice remains uncertain. There are many possible reasons for this, but almost certainly a major factor is that most studies have adopted mortality or morbidity as primary end points thereby necessitating the recruitment of very large patient numbers. We have previously demonstrated that gut function determined by tolerance of enteral feeds is common in postoperative and critically ill patients and does impact independently on prognosis (Gatt *et al*., 2007). On this background and taking the return of normal gastrointestinal function as our primary endpoint, the rationale for this study was that a selection of purposely chosen GSNs might, based on their cumulative effect, be more likely to manifest difference in the return of gut function.

At the time of commencement of this study, there was no commercially available GSN preparation which had the desired constituents and properties necessary to fit the study

design. After a critical review of the literature, a cocktail of GSN was specifically put together so as to provide only the desired preparations at the required doses. As the GSN were to be dispensed for a month, it was also considered necessary to be able to administer the preparations orally or down an NGT, and in as small a volume as possible to encourage tolerance and compliance. Four separate preparations were included into the final GSN cocktail: pre- and probiotics as they have been shown to beneficially modulate the gastrointestinal microflora, (Rastall, 2004; Reddy *et al*., 2007[b]), multivitamin and antioxidant preparation as these attenuate oxidant stress and decrease ischaemia-reperfusion injury (Baines and Shenkins, 2002; Molyneux, Glyn and Ward, 2002; Duggan, Gannon and Walker, 2002) and finally glutamine, because it is recognised as being the preferred fuel substrate for the enterocytes as well as having other desirable gut-specific effects (Wischmeyer, 2005; Wischmeyer, 2007). The evidence for the benefits of enterally administered glutamine is weaker than that for its intravenous administration. In an attempt to curtail costs, decrease the daily enteral volume necessary for GSN administration, and above all to improve efficacy of the GSN cocktail, glutamine was administered parenterally for the first seven days, and then orally for the remainder. Arginine was specifically excluded from the cocktail because of isolated reports of detrimental outcomes in the critically ill septic patient (Bertolini *et al*., 2003).

A potential criticism of this study is that the dosages of GSNs employed may be considered too low on the basis of evidence available now that was not in the literature at the time this study was designed. We recognise that higher GSN concentrations, as recommended in more recent literature, might produce further enhancement of gut

function that might have been associated with changes in one or other of our secondary endpoints.

There is little doubt that nutrition effects immunity (Johnson and Kudsk, 1999). Well-nourished patients sustain fewer complications and recover from infection and illness faster than malnourished patients (Windsor and Hill, 1988). Protein energy malnutrition develops rapidly during critical illness, which if prolonged and progressive impairs host immune and antibacterial defences (Deitch *et al*., 1987; Deitch *et al*., 1990[b]), disrupts the normal ecology of the resident microflora (Deitch *et al*., 1987; Chandra and Gupta, 1991), and may produce changes in mucosal architecture and mucosal mass (Bragg, Thompson and Rikkers, 1991; Tappenden, 2006). It is, therefore, somewhat surprising that adjuvant nutritional support, whether enteral or parenteral, has not been consistently shown to be associated with improvements in clinical outcome particularly in critically ill patients. In this study, there were no differences in the adequacy of feeding or basic nutritional characteristics between the groups. It is not possible to attribute differences in outcome between the two to variations in nutrition. One of the strengths of the study design is the incorporation of optimal nutritional practices. This ensured that more patients achieved their nutritional requirements (Woodcock and MacFie, 2002; Chahal *et al*., 2004; Woodcock and MacFie, 2004), and therefore decreased the likelihood of there being a confounding factor of GSN acting simply as nutrients in the setting of malnutrition. In other words, optimal nutrition helped to ensure that observed differences between the study arms related to the gut-specific effects of GSN and not to their effects as simple nutrients.

The recognised importance of nutrition on immunity together with an inability to decrease the prevalence of deaths in the critically ill caused by delayed sepsis and MOF has led to increasing interest in immunomodulating preparations, and in particular, the use of immunonutrients. These are substrates specifically designed to stimulate the immune response on the theoretical grounds that they will assist the recovery of immunocompromised patients. Many studies investigating the use of immunonutrients have now been reported and their results reviewed (Heys *et al*., 1999; Heyland *et al*., 2001[b]; Montejo *et al*., 2003; Beale *et al*., 2008). Suffice to say there is again no consistent evidence of benefit with some studies showing improvements in outcomes (Bowler *et al*., 1995; Galban *et al*., 2000; Beale *et al*., 2008) but others a significant deterioration (Bertolini *et al*., 2003). There are many possible explanations for the discrepancies observed in the results of these studies. Most are underpowered for the primary endpoints employed, feeding regimens are inconsistent between control and study groups, blinding is often absent, enteral and parenteral nutrition are often used inappropriately, and gut function is rarely assessed objectively since, until recently, no validated quantifiable definition for it existed in the literature. Unlike similar studies, the primary outcome of this trial was the return of gut function using a quantifiable and therefore objective measure based on enteral tolerance. This method of assessment of gut function has been previously validated (Gatt *et al*., 2007).

The findings of this study demonstrate that the return of adequate gut function can be expedited with the use of GSN. The administration of GSN was also noted to have other benefits on patient outcomes which included an attenuation of the acute phase response,

decreased septic complications, and possibly improved survival, albeit the latter being non-significant in this study. While a mortality rate of 28% in the control arm may be perceived as excessive for patients with a median APACHE II score of 10, one must be mindful that all patients in this study had evidence of gut failure at recruitment. In other words, the control cohort was not representative of all patients with an APACHE II score of 10. On the contrary, they were only representative of that sub-group of patients with an APACHE II score of 10 that in addition manifested IF. The relevance of this observation is that while APACHE II takes into consideration most organ failures, it does not score for factors relating to gut failure. However, since IF is independently associated with outcome, APACHE II effectively disregards the effects of gut function on patient prognosis and probably explains the high mortality of 28% despite a relatively low APACHE II score.

It is self-evident that failure to treat an organ dysfunction will have deleterious effects on patient outcome. The difference in mortality between groups in this study, albeit statistically insignificant, was approximately threefold. In this respect, it is relevant to note that it has previously been shown that the NNT for patients with gut failure was 1.504 (Table 5.6). In other words, for every 3 patients in who gut failure is treated effectively, 2 will be predicted to survive. Extrapolating from this observation, of the 7 patients (28% of cohort) who died in the untreated arm, two thirds of these (approximately 5 patients) would have been expected to survive with adequate treatment of their IF. While the study was not powered to assess differences in survival between the two groups, the documented mortality of 7 patients (28%) in the control arm and of 2

patients (8%) in the intervention arm is consistent with previous work relating to the effect of gut failure on outcome and with the fact that APACHE II does not score for gut failure despite its independent association with patient outcome.

Whether the attenuation of the acute phase response, decreased septic complications, and improved absolute survival noted in this study were simply a result of GSN administration, or alternatively a consequence of an earlier return of normal gut function brought about by GSN cannot be confidently concluded from this study. However with the gut representing the single largest immunological and cytokine producing organ in the body, it is interesting to note many similarities in the findings from this study and the results of other trials investigating the gut origin of sepsis hypothesis.

Deitch proposes a central role of the gut in propagating the cytokine imbalance eventually resulting in SIRS, MOF and death (Cohen *et al.*, 2004). Marshall, on the other hand, describes the gut as the 'undrained abscess of multiorgan failure' (Marshall, Christou and Meakins, 1993). It remains unclear whether failure of the gut, together with dysfunction of its barrier and immunological roles, initiates or simply propagates MOF and death. What is evident from daily clinical practice, however, is that the treatment of delayed sepsis in the critically ill is often unsuccessful despite ongoing advances in critical care and the availability of new broader-spectrum antimicrobial therapies. Critically ill patients more commonly than not succumb to this insult, possibly because the overwhelming sepsis is not the cause of their demise, but simply a sign of underlying gut failure (which defies both detection and effective treatment). Findings from this study

support the hypothesis that gastrointestinal dysfunction, much like other single organ failures, predisposes to disease. As a consequence, the curtailing of gut dysfunction and the attenuation of the acute phase response, in this case by the administration of GSN, might represent the mechanisms for improved outcomes in the intervention arm of this study.

8.5 CONCLUSION

In conclusion, results of this study demonstrate that the use of GSN expedites the return of gut function. This was associated with an attenuation of the acute phase response, decreased rates of sepsis, and possibly improved survival, albeit not significant. Whether these beneficial outcomes came about as a result of the enhanced recovery of gut function or were only associated with it remains unclear. The prognostic advantage of an earlier return of gut function makes theoretical sense and the results of larger studies are awaited to confirm survival benefit.

CHAPTER 9:
CONCLUSION & FUTURE RESEARCH

'All diseases begin in the gut.

Death sits in the bowel,

a bad digestion is the root of all evil.'

Hippocrates,
c. 460 - 370 BC

9.1 RATIONALE FOR THIS RESEARCH

The overarching aims of this thesis were to investigate the importance of gut function and subsequent failure as an indicator of clinical outcome, derive a definition for this phenomenon, and then develop a strategy to treat it. A scoping review of relevant literature found that supporting evidence for the role of the gut as the motor which drives disease, MOF and death can be drawn from a variety of seemingly unrelated sources in the medical and surgical literature. Studies investigating the so-called 'gut origin of sepsis hypothesis' and BT provided strong support for this contention, Additional evidence could be drawn from trials assessing enhanced recovery programmes after surgery as well as from papers relating to various aspects of human nutrition. However, from this evidence, it became apparent that definitive proof of the importance of underlying gut function on clinical outcome is hindered by the absence of a quantifiable definition for the state of gut function. More specifically, there existed no definition for what constitutes adequate gut function as distinguishable from a state of gut failure.

The literature review in chapter 1 highlighted at least three main areas of insufficiency in the literature. Firstly, how can one distinguish adequate gastrointestinal function from bowel insufficiency (i.e. gut failure)? Secondly, much like other single organ failures, is gut failure associated with poorer outcomes? Thirdly, can gut failure be treated, and if so what effects does this have on outcomes?

This theses set out to investigate these issues by means of a series of clinical studies

carried out by the author. This chapter summarises the findings of these clinical trials.

9.2 SUMMARY OF RESEARCH FINDINGS

The first study in chapter three was set up to investigate the merits of a gut-directed multimodal optimization package on patients undergoing major colorectal surgery in the setting of a randomized clinical study. The effects on the recovery of postoperative gut function were also recorded. From this trial, it was evident that enhanced recovery programmes benefited patients undergoing elective colorectal surgery by curtailing the need for urinary catheterisation, expediting postoperative mobilization, and allowing patients to tolerate fluids and diet sooner than controls who were receiving traditional surgical care. In addition, optimization enhanced the return of normal gut function and decreased the period of hospitalisation without any measurable increases in morbidity or mortality. This study corroborated evidence that gut function is important to patient outcomes, but also highlighted the difficulties in the interpretation of data relating to gastrointestinal function because of the lack of an objective definition for adequate as distinct from IGF.

Conclusion 1: Multimodal optimization improved outcomes and this may relate to an earlier recovery of gut function

Having established the need for an objective definition of the state of gut function, the two studies described in chapter 4 set out to achieve this. The main aim was to develop a definition for adequate gut function as distinct from gut failure which was quantifiable, objective, reproducible, evidence-based, pragmatic, easily applicable by the bedside, and associated with patient outcome. This was achieved by associating the tolerance of varying amounts of nutritional intakes by the gut for different time periods with prognosis. In the first of these studies, the tolerance by the gut of 70, 80 and 90 per cent of calculated nutritional requirements were sequentially associated with prognosis. The value of 80 per cent was considered to represent the best trade off between specificity, sensitivity, positive and negative predictive values of outcome. The subsequent study built on these results by asking how long a patient needed to tolerate ≥80% of their calculated nutritional requirements to be deemed as having adequate gut function. Similarly, the methodology employed involved the association of enteral tolerance with outcome. The study concluded that a continuous period of ≥48 hours enteral tolerance was the optimal test for gut function. In other words, patients whose gut tolerated ≥80% of their calculated nutritional requirements for a continuous period of ≥48 hours could be said to have adequate gut function. By inference, anything less than this would represent gastrointestinal insufficiency, a state of gut failure.

Conclusion 2: Adequate gut function can be defined by the oral or enteral tolerance of ≥80% of calculated nutritional requirements for a minimum continuous period of 48 hours or more. Anything less represents gut failure and is associated with a poorer prognosis.

However, a vast number of factors are known to influence patient outcome. These include patient age, the emergence of complications, and the presence of other single organ failures. To demonstrate that gut failure was independently associated with outcome, it was necessary to correct for as many variables as possible that influenced prognosis. This validation process was the aim of the fourth study presented in chapter 5. A large number of variables that may have influenced outcome were prospectively recorded from 315 patients receiving adjuvant nutritional support. This permitted univariate identification of a number of factors associated with outcome followed by multivariate analysis of these factors. Multivariate analysis showed that in this cohort of patients, gut failure was associated with outcome even when correcting for the effects of all the other variables. In other words, gut failure was independently associated with patient outcome. A sample size calculation suggested generalizability of these findings.

<u>Conclusion 3</u>: Gut failure, defined by oral/enteral intolerance is independently associated with outcome.

One issue in particular about the established definition of gut function still needed clarification. If tolerance defines whether the gut functions or not, then anything that may influence feed tolerance may be said to also influence gut function. The delivery of feed beyond the pylorus is popularly believed to enhance feed tolerance over intragastric feeding. A problem with all the studies in the literature comparing pre- and postpyloric feeding is the fact that they do not consider the major drawback of the latter modality of

feeding, namely the difficulty and consequently the extra time necessary to achieve postpyloric tube placement, with the inevitable delays this has on the instigation of feeding. In other words, all studies in the literature comparing pre- and postpyloric feeding are biased in favour of postpyloric feeding. Two studies were therefore necessary to investigate the effects of feeding beyond the pylorus on enteral tolerance. These are described in chapter 6. In the first study, a novel bedside technique of postpyloric tube placement was developed and validated so as to do away with delays in postpyloric tube placement associated with transfer to the radiology or endoscopy departments. Using this technique, just over 80 percent of tubes could be placed beyond the pylorus. Subsequent to this, a second study was performed employing this technique of tube placement. This second study compared pre- and postpyloric feeding within the remits of a randomized and controlled clinical trial. The bedside technique allowed for similar time delays till the instigation of feeding between the two groups. As such this technique permitted the design of an unbiased study comparing the two modalities of nutrition. The results of this study showed that the number of patients who achieved enteral tolerance in both groups was similar irrespective of whether patients were fed into the stomach or beyond. The definition of gut function did not need to incorporate corrections for the site of enteral feed delivery.

Conclusion 4: The site of delivery of nutrients, be this pre- or postpyloric, is not associated with enhanced enteral tolerance or gut function.

Gut function may also be investigated by assessing splanchnic blood flow and how this varies with different modalities of feeding. It is widely recognised that enteral perfusion increases to meet the demands of an oral or enteral food challenge, but no studies have investigated the effects of TPN on SMA flow in man. This was addressed in a qualitative before-and-after study described in chapter 7. The aim of this study was to observe changes in SMA perfusion associated with oral, enteral and parenteral challenges. The results of this study showed that when compared to fasting levels of SMA blood flow, splanchnic perfusion increased in all individuals subjected to an oral or enteral challenge, but decreased universally in patients receiving TPN. This may suggest a therapeutic role for nutritional support as a means of modulating gut perfusion.

Conclusion 5: An enteral food challenge increases SMA blood flow while parenteral nutrition administration decreases splanchnic perfusion. This may have therapeutic implications by allowing nutritional manipulation of gut perfusion.

The final study in this series of clinical trials is described in chapter 8. This study addressed the issue of modulation of gut function and failure. The basic argument behind this study is that if one accepts that gut function is indeed independently associated with outcome, then might it be possible to enhanced recovery of gut function and would this, in turn, be associated with demonstrable clinical improvements?

It was unclear whether gut function, as defined by enteral tolerance, could be modulated in the first place. For this reason, a gut-directed therapy consisting of a number of GSN was put together by the author and investigated. This cocktail of GSN was administered to critically patients with evidence of gut failure. The setting was that of an externally randomized, double-blind, and placebo-controlled clinical trial. The primary aim of this study was to assess whether the cocktail of GSN had an effect on the time to return of normal gut function. A subsidiary aim was to record the consequences, if any, of the modulation of gut function on clinical outcomes.

The results of this study demonstrated that the use of GSN was associated with an earlier return of gut function, and improved outcomes. Patients receiving GSN were noted to have a diminished chance of developing septic complications, they demonstrated an attenuation of the acute phase response, as well as a decrease in the absolute number of deaths at three months, albeit not significant. Whether these beneficial outcomes came about as a result of the enhanced recovery of gut function or whether they were only associated with a curtailed period of gut failure remains unclear.

<u>Conclusion 6</u>: The administration of GSN was associated with an enhanced recovery of gut function and a commensurate improvement in other clinical outcomes.

9.3 FULFILMENT OF THE AIMS OF THE THESIS

Taken together, the findings from the eight studies presented in this work fulfil the aims of the thesis. The importance of gut function on clinical outcomes is emphasised, and the deficiencies in the relevant medical literature are highlighted, in particular the need to define adequate gastrointestinal function and gut failure. The research continues by developing such a definition and then validating it by demonstrating its independent association with prognosis.

Potential issues in the established definition are then interrogated, specifically by addressing the importance of the site of enteral feed delivery on enteral tolerance (pre-*versus* postpyloric feeding) and the effects of different modalities of nutritional treatment (oral, enteral and parenteral) on splanchnic flow. In the process, a novel bedside technique for postpyloric tube placement was developed. Allowance for changes in the site of feed delivery was not felt to be necessary when defining the state of gut function.

Finally, the question of whether gut function could be modulated and whether this was to the advantage of patients was considered. A gut-directed therapy was developing and implementsed. Using this therapy, a cocktail of GSN were able to expedite the return of normal gut function over placebo, and that this in turn was associated with direct benefits to clinical outcomes. The aims of the thesis were fulfilled. Within the limitations of these eight trials, the cause-effect loop for the effects of gut failure on outcome were established and verified.

9.4 CONCLUSION: CLINICAL RELEVANCE OF THE FUNCTIONAL STATE OF THE GUT

There is mounting evidence that the state of gut function, much like that of other organs, effects patient outcome. A more comprehensive understanding of how the state of gastrointestinal function affects human physiology represents both a compelling challenge to clinical research as well as a tremendous opportunity for improving care.

The overall conclusion of this thesis is that gut function, as defined by enteral tolerance, is independently associated with patient prognosis. Modulation of gut function is possible with apposite therapies, and this is, in turn, associated with commensurate improvements in outcome. Further work will need to be carried out to confirm these findings.

9.5 FUTURE RESEARCH

Findings from the work in this thesis have highlighted a number of areas that require further investigation. Areas of possible future research include:

- Validation of the work performed in this thesis: All the work that has been presented is from one institution. For purposes of scientific validity, the ability of other researchers to reproduce the findings of these studies would add increased legitimacy to the observations made.

- Investigations to elucidate the mechanisms by which ERAS programs bring about improvements in the postoperative patient: A better understanding of the mechanisms involved in patients on ERAS programs may shed light on those interventions that are of actual clinical relevance. Current literature makes it impossible to point to the relative value of one intervention over another. In this respect, ERAS trials in which groups differ by only one intervention (such as the use of laparoscopic techniques, the provision of detailed written and verbal preoperative information, or the use of Doppler-guided perioperative fluid administration) are eagerly awaited. Such studies are currently being undertaken in various units including our own institution.

- Further interrogation of the established definition of gut dysfunction: A limitation of defining the state of gastrointestinal function in terms of enteral tolerance is that gut failure becomes an all-or-nothing event. Incorporation of indicators of severity into this definition may prove useful and help to guide future treatment.

- Additional assessments of gut kinetics: Assessments of gut function based on enteral tolerance rely on the adequate cranio-caudal propulsion of food by co-ordinated gut peristalsis. Kinetic studies which investigate both mechanical migratory motor complexes as well as electrical activity in the gut and then relate this activity to enteral tolerance may add important insights into the mechanisms involved in gut failure and the recovery of gut function.

- Establishing other methods of distinguishing adequate gut function from IF: In

daily clinical practice, distinguishing normal organ function from failure can be achieved by implementing one of a number of accepted definitions. For example, renal failure can be defined in terms of glomerular filtration rates, serum creatinine levels, and rates of urine formation, but to name a few examples. The specific clinical setting then allows for the most appropriate definition to be chosen to make this distinction between, in this case, adequate renal function and renal failure. This thesis sets out to validate the distinction between adequate and inadequate gut function based on the phenomenon enteral tolerance. The ability to validate other methods to assess gut function may be clinically useful. In this respect, the use of specific probe absorption assays may hold some promise, but the relevance of these assays on outcome remains to be validated.

- Elucidating the mechanisms which promote deterioration and death in patients with gut failure: Defining specific immunological pathways and measurement of specific cytokine levels associated with gut failure may be necessary to better understand the mechanisms involved.

- Investigating the role of nutritional therapy as a method of modulating gut perfusion: The finding that enteral feeding upregulates splanchnic perfusion while TPN decreases SMA flow may hold therapeutic potential. It remains to be established whether nutritional therapies may be harnessed to modulate splanchnic blood flow.

- Investigating other factors which effect gut perfusion: It is plausible that

numerous constitutional factors (such as gender, age and BMI) as well as extrinsic factors (such as drugs, constitution and quantity of nutrition) effect splanchnic blood flow in vivo. A better understanding of the impact of these variables on gut perfusion is necessary in man. Additionally, the relative importance and clinical significance of different methods of assessing gastrointestinal perfusion in vivo (such as DUS, dilutional techniques and mucosal pH assessments) needs clarification.

- Larger scale studies looking at the effects of cocktails of GSN on decreasing mortality: The study described in this thesis (chapter 8) was underpowered to accurately assess the secondary end point of mortality. Larger studies will be necessary to investigate the effects of GSN on prognosis.

- The development of other gut-directed therapies: One therapy (i.e. GSN) for the treatment of gut failure is likely to have limited success in effectively treating this deleterious condition. Similar to the management of other organ failures, a wide range of therapies aimed at curtailing gut failure and enhancing the return of normal gut function need to be developed and validated. These strategies may take the form of a number of interventions grouped together in an attempt to enhance the return of gut function or attenuate the period of gut failure similar to multimodal optimization strategies in the postoperative patient.

APPENDICES

Appendix 1: Publications & abstracts

Appendix 2: Recognition for work from this thesis

Appendix 3: Scoring systems & questionnaires

Appendix 4: Estimating nutritional requirements

Appendix 5: Constituents of feeds & multivitamins

APPENDIX 1: PUBLICATIONS & ABSRACTS

Publications: *(presented in reverse chronological order)*

MacFie J and Gatt M. (2007) L-alanine-L-glutamine supplementation improves the outcome after colorectal surgery for cancer. *Colorectal Dis.* 9(9): 853; author reply 853-854.

Finan PJ, Campbell S, Verma R, MacFie J, Gatt M, Parker MC, Bhardwaj R, Hall NR. (2007) The management of malignant large bowel obstruction: ACPGBI position statement. *Colorectal Dis.* Suppl 4:1-17.

Gatt M and MacFie J. (2007) Randomized clinical trial of the impact of early enteral feeding on postoperative ileus and recovery (*Br J Surg*. 2007; 94: 555-561). *Br J Surg.* 94(8):1045.

Reddy BS, MacFie J, Gatt M, Larsen CN, Jensen SS, Leser TD. (2007) Randomized clinical trial of effect of synbiotics, neomycin and mechanical bowel preparation on intestinal barrier function in patients undergoing colectomy. *Br J Surg.* 94(5): 546-554.

Gatt M, Reddy BS, MacFie J. (2007) Bacterial Translocation in the Critically Ill: A Review of the Evidence and Methods of Prevention. *Aliment Pharmacol Ther*. 25(7): 741-757.

Reddy BS, MacFie J, Gatt M, Macfarlane-Smith L, Bitzopoulou K, Snelling AM. (2007) Commensal bacteria do translocate across the intestinal barrier in surgical patients. *Clin Nutr.* 26(2): 208-215.

Reddy BS, Gatt M, Sowdi R, MacFie J. (2006) Surgical manipulation of the large intestine increases bacterial translocation in patients undergoing elective colorectal surgery. *Colorectal Dis.* 8(7): 596-600.

Gatt M and MacFie J. (2006) Randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection. *Br J Surg.* 93(7): 891.

Rao MM, Gatt M, Kallam R, MacFie J. (2006) Impact of oedema on recovery after major abdominal surgery and potential value of multifrequency bioimpedance measurements. *Br J Surg.* 93: 769-770.

MacFie J, Reddy BS, Gatt M, Jain PK, Sowdi R, Mitchell CJ. (2005) Bacterial translocation studied in 927 patients over 13 years. *Br J Surg.* 93: 87-93.

Gatt M, Anderson ADG, Reddy BS, Hayward-Sampson P, Tring IC, MacFie J. (2005) Randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection. *Br J Surg.* 92: 1354-1362.

Gatt M and MacFie J. (2005) Bacterial translocation in surgical patients. In: *Recent Advances in Surgery Ed. 28*. pp. 23-32. London: The Royal Society of Medicine Press Limited.

Gatt M and MacFie J. (2005) Fast-track surgery. *Br J Surg.* 92: 494.

Published abstracts: *(not yet published as papers – in reverse chronological order)*

Gatt M, MacFie J, Coppack A, McNaughton L, Yassin N, Rao MM, Kallam R. (2007) Gut-specific nutrients may be used to enhance the recovery of gut function in the critically ill: results of a double-blind, placebo-controlled, randomized clinical trial. *Clin Nutr.* Suppl 2: 24.

Gatt M, MacFie J, McNaughton L, Coppack A, Rao MM, Kallam R, Ramsey C. (2007) Gut function is an independent indicator of patient outcome: proof of principle. *Clin Nutr.* Suppl 2: 108.

Kallam R, Reddy BS, Rao MM, Gatt M, Mitchell CJ, MacFie J. (2007) Gastric colonisation in surgical patients: an indicator of altered gut barrier function. *Clin Nutr.* Suppl 2: 15.

Kallam R, Reddy BS, Rao MM, Gatt M, MacFie J. (2007) Specific identification of live probiotic organism *Bifidobacterium animalis* subspecies lactis from faecal samples of surgical patients by fluorescent colony hybridisation assay. *Clin Nutr.* Suppl 2: 45-46.

Rao MM, Kallam R, Flindall I, Gatt M, MacFie J. (2007) Changes in whole gut permeability following elective colorectal resections. *Clin Nutr.* Suppl 2: 122-123.

Rao MM, Gatt M, Kallam R, Flindall I, MacFie J. (2007) Gut specific nutrients in patients undergoing elective surgery: a prospective randomised trial. *Clin Nutr.* Suppl 2: 60-61.

Rao MM, Kallam R, Flindall I, Gatt M, MacFie J. (2007) Predicting the return of gut function using gastric emptying studies. *Clin Nutr.* Suppl 2: 26.

Rao MM, Kallam R, Flindall I, Gatt M, MacFie J. (2007) The role of perioperative fluid balance on postoperative outcomes after elective colonic resection in the setting of multimodal optimization. *Clin Nutr.* Suppl 2: 123.

Kallam R, Reddy BS, Rao MM, Gatt M, Mitchell CJ, MacFie J. (2007) Gastric colonisation in surgical patients. *Br J Surg.* 94 Suppl 2: 79-198.

Grover K, Gatt M, Anderson ADG, Fleming SC, Mitchell CJ and MacFie J. (2006) The effects of severity of acute pancreatitis on whole gut permeability. *Br J Surg*. 93(S1): 40–57.

Gatt M, Coppack A, McNaughton L, Ramsey C, Wallace L, Mitchell CJ, MacFie J. (2005) Pre vs. postpyloric feeding: a randomized clinical trial. *Clin Nutr.* 24: 697-698.

Gatt M, Reddy BS, Barandiaran J, Mitchell CJ, MacFie J. (2005) Bedside postpyloric feeding tube insertion: a randomised trial to validate this technique. *Clin Nutr.* 24: 697.

Gatt M, Reddy B, Coppack A, McNaughton L, MacFie J. (2005) Pre vs. postpyloric feeding tubes: patients' perspective of discomfort. *Clin Nutr.* 24: 697.

Gatt M, Coppack A, McNaughton L, Grover K, Mitchell CJ, MacFie J. (2005) Enteric aspirate pH is a poor indicator of fine bore feeding tube position. *Clin Nutr.* 24: 698.

Gatt M, Suppiah A, Barandiaran J, Coppack A, McNaughton L, Perry EP, MacFie J. (2005) Prevalence of nutritional measurement documentation prior to the introduction of the malnutrition universal screening tool. *Clin Nutr.* 24: 550.

Grover K, Gatt M, Reddy BS, Anderson ADG, Fleming SC, Mitchell CJ, MacFie J. (2005) Whole gut permeability in acute pancreatitis. *Br J Surg.* 92(Supp 1): 140-143.

Chahal H, Anderson ADG, Gatt M, McNaughton L, Ramsay C, Richardson V, MacFie J. (2004) An audit of optimal nutrition. *Clin Nutr*. 23: 909-928.

APPENDIX 2: RECOGNITION FOR WORK FROM THIS THESIS

- **Moynihan Prize**, ASGBI, Manchester 2007
  Gatt M, MacFie J, McNaughton L, *et al*. (2007) Gut function is an independent prognostic indicator and can be modulated to benefit patient outcome: proof of principle. *Br J Surg.* 94 Suppl 2: 1-78
  Presented at ASGBI, Manchester, 2007

- **Moynihan Prize**, ASGBI, Glasgow 2005
  Reddy BS, Gatt M, Snelling AM, *et al.* (2005) Enteric bacteria do translocate: proof at last. *Br J Surg.* 92 (Supp 1): 1-3.
  Presented at ASGBI, Glasgow, 2005

- **ESPEN 2005 Travel Fellowship**, ESPEN, Brussels 2005
  Gatt M, Coppack A, McNaughton *et al*. (2005) Pre vs. postpyloric feeding: a randomized clinical trial. *Clin Nutr.* 24: 697-698
  Presented at ESPEN, Brussels 2005

- **Acute Clinical Team of the Year, Chief Executives' Quality & Innovation Award**, Scarborough & NE Yorkshire Healthcare NHS Trust and Scarborough, Whitby & Ryedale PCT, 2005
  Awarded for the development, validation and implementation of a system for multimodal optimization of perioperative care for colorectal patient across the hospitals of this Trust.

- **Leeds Regional Surgical Prize**, Leeds, 2005
  Reddy BS, MacFie J, Gatt M, *et al*. Randomized controlled study on the effects of probiotics, neomycin and mechanical bowel preparation on gut barrier function in elective surgical patients.
  Presented at the Leeds Regional Surgical Club, Leeds, November 2005

- **Leeds Regional Surgical Prize**, Scunthorpe, 2004
  Gatt M, Anderson ADG, McNaught CE, *et al*. Multimodal optimization of surgical care: A randomized controlled trial in patients undergoing major colonic resection.
  Presented at the Leeds Regional Surgical Club, Scunthorpe, 2004

APPENDIX 3: SCORING SYSTEMS AND QUESTIONNAIRES

ASA Grading

ASA Grade	Definition
I	Normal healthy individual
II	Mild systemic disease that does not limit activity
III	Severe systemic disease that limits activity but is not incapacitating
IV	Incapacitating systemic disease which is constantly life-threatening
V	Moribund, not expected to survive 24 hours with or without surgery

Figure iii.1: The ASA grading system.

APACHE II Scoring System

	Acute physiology score								
	High normal range					*Low normal range*			
Variable	*+4*	*+3*	*+2*	*+1*	*0*	*+1*	*+2*	*+3*	*+4*
Temperature (°C)	>41	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	<29.9
Mean arterial pressure (mm Hg)	>160	130–159	110–129		70–109		50–69		<49
Heart rate (ventricular; beats/min)	>180	140–179	110–139		70–109		55–69	40–54	<39
Respiratory rate	>50	35–49		25–34	12–24	10–11	6–9		<5
Oxygenation (mm Hg)									
A_{aDO_2} when F_{iO_2} >0.5	>500	350–499	200–349		<200				
P_{aO_2} when F_{iO_2} <0.5					PO_2 >70	PO_2 61–70		PO_2 55–60	PO_2 <55
Arterial pH	>7.7	7.6–7.69		7.5–7.59	7.33–7.49		7.25–7.32	7.15–7.24	<7.15
Serum Na (mmol/l)	>180	160–179	155–159	150–154	130–149		120–129	11–119	<110
Serum K (mmol/l)	>7	6–6.9		5.5–5.9	3.5–5.4	3–3.4	2.5–2.9		<2.5
Serum creatinine (mg/100 ml) Double score for ARF	>3.5	2–3.4	1.5–1.9		0.6–1.4		<0.6		
Packed cell volume (%)	>60		50–59.9	46–49.9	30–45.9		20–29.9		<20
While blood cell count ($\times 10^3/mm^3$)	>40		20–39.9	15–19.9	3–14.9		1–2.9		<1
Glasgow coma scale*									

*Score = 15 − actual Glasgow coma scale.

The APACHE II score is given by the sum of the acute physiology score, the age (in years) points, and the chronic health points. Age points are assigned as follows: 0, <44; 2, 45–54; 3, 55–64; 5, 65–74; and 6, >75. Chronic health points are assigned if the patient has a history of severe organ system insufficiency or is immunocompromised, as follows: 5, non-operative or emergency postoperative patients; 2, elective postoperative patients. Organ insufficiency or an immunocompromised state must have been evident before admission to hospital and must conform to the following criteria: *liver*, biopsy confirmed cirrhosis and documented portal hypertension, episodes of past upper gastrointestinal bleeding attributed to portal hypertension, or prior episodes of hepatic failure/encephalopathy/coma; *cardiovascular*, New York Heart Association Class IV (that is, symptoms of angina or cardiac insufficiency at rest or during minimal exertion); *respiratory*, chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction—that is, unable to climb stairs or perform household duties, or documented chronic hypoxia, hypercapnia, secondary polycythaemia, severe pulmonary hypertension (>40 mm Hg), or respirator dependency; *renal*, receiving chronic dialysis; and *immunocompromised*, the patient has received treatment that suppresses resistance to infection—for example, immunosuppression, chemotherapy, radiotherapy, long term, high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, such as leukaemia, lymphoma, AIDS. A_{aDO_2}, alveolar–arterial oxygen difference; P_{aO_2}, arterial partial pressure of oxygen; F_{iO_2}, fraction of inspired oxygen; ARF, acute renal failure.

Figure iii.2: The APACHE II scoring system (adapted from Knaus *et al.*, 1985).

POSSUM Scoring System

Physiological score (to be scored at the time of surgery)

	Score			
	1	2	4	8
Age (years)	≤60	61–70	≥71	
Cardiac signs	No failure	Diuretic, digoxin, antianginal or hypertensive therapy	Peripheral oedema; warfarin therapy	Raised jugular venous pressure
Chest radiograph			Borderline cardiomegaly	Cardiomegaly
Respiratory history	No dyspnoea	Dyspnoea on exertion	Limiting dyspnoea (one flight)	Dyspnoea at rest (rate ≥30/min)
Chest radiograph		Mild COAD	Moderate COAD	Fibrosis or consolidation
Blood pressure (systolic) (mmHg)	110–130	131–170 100–109	≥171 90–99	– ≤89
Pulse (beats/min)	50–80	81–100 40–49	101–120	≥121 ≤39
Glasgow coma score	15	12–14	9–11	≤8
Haemoglobin (g/100 ml)	13–16	11·5–12·9 16·1–17·0	10·0–11·4 17·1–18·0	≤9·9 ≥18·1
White cell count ($\times 10^{12}$/l)	4–10	10·1–20·0 3·1–4·0	≥20·1 ≤3·0	
Urea (mmol/l)	≤7·5	7·6–10·0	10·1–15·0	≥15·1
Sodium (mmol/l)	≥136	131–135	126–130	≤125
Potassium (mmol/l)	3·5–5·0	3·2–3·4 5·1–5·3	2·9–3·1 5·4–5·9	≤2·8 ≥6·0
Electrocardiogram	Normal		Atrial fibrillation (rate 60–90)	Any other abnormal rhythm or ≥5 ectopics/min Q waves or ST/T wave changes

COAD, chronic obstructive airways disease

Operative severity score. (Definitions of surgical procedures with regard to severity are guidelines; not all procedures are listed and the closest should be selected)

	Score			
	1	2	4	8
Operative severity*	Minor	Moderate	Major	Major+
Multiple procedures	1		2	>2
Total blood loss (ml)	≤100	101–500	501–999	≥1000
Peritoneal soiling	None	Minor (serous fluid)	Local pus	Free bowel content, pus or blood
Presence of malignancy	None	Primary only	Nodal metastases	Distant metastases
Mode of surgery	Elective		Emergency resuscitation of >2 h possible† Operation <24 h after admission	Emergency (immediate surgery <2 h needed)

*Surgery of moderate severity includes appendicectomy, cholecystectomy, mastectomy, transurethral resection of prostate; major surgery includes any laparotomy, bowel resection, cholecystectomy with choledochotomy, peripheral vascular procedure or major amputation; major+ surgery includes any aortic procedure, abdominoperineal resection, pancreatic or liver resection, oesophagogastrectomy; †indicates that resuscitation is possible even if this period is not actually utilized

Figure iii.3: The POSSUM scoring system (adapted from Copeland *et al.*, 1991)

Sequential Organ Failure (SOFA) Score

The SOFA score evaluate status of the following organ systems separately:

1. Respiration

2. Coagulation

3. Liver

4. Cardiovascular

5. Central Nervous System

6. Renal

1. Respiration

PaO_2/FiO_2, mmHg	SOFA score
< 400	1
< 300	2
< 200	3
< 100	4

2. Coagulation

Platelets×10^3/mm^3	SOFA score
< 150	1
< 100	2
< 50	3
< 20	4

3. Liver

Bilirubin, mg/dl	SOFA score
1.2 – 1.9	1
2.0 – 5.9	2
6.0 – 11.9	3
> 12.0	4

4. Cardiovascular

PaO_2/FiO_2, mmHg	SOFA score
< 400	1
< 300	2
< 200	3
< 100	4

5. Central Nervous System

Glasgow coma score	SOFA score
13 – 14	1
10 – 12	2
6 – 9	3
< 6	4

6. Renal

Creatinine, mg/dl (or urine output)	SOFA score
1.2 – 1.9	1
2.0 – 3.4	2
3.5 – 4.9 (or < 500 ml/d)	3
> 5.0 (or < 200 ml/d)	4

Figure iii.4: The Sequential Organ Failure (SOFA) Score

Glasgow Coma Score (GCS)

The GCS is scored between 3 and 15, 3 being the worst, and 15 the best. It is composed of three parameters : Best Eye Response, Best Verbal Response, Best Motor Response, as given below :

Best Eye Response. (4)

1. No eye opening.
2. Eye opening to pain.
3. Eye opening to verbal command.
4. Eyes open spontaneously.

Best Verbal Response. (5)

1. No verbal response
2. Incomprehensible sounds.
3. Inappropriate words.
4. Confused
5. Orientated

Best Motor Response. (6)

1. No motor response.
2. Extension to pain.
3. Flexion to pain.
4. Withdrawal from pain.
5. Localising pain.
6. Obeys Commands.

Figure iii.5: The Glasgow Coma Scale (GCS)

Hospital Anxiety and Depression (HAD) Scale

Patients are asked to choose one response from the four given for each interview. They should give an immediate response and be dissuaded from thinking too long about their answers. The questions relating to anxiety are marked "A", and to depression "D". The score for each answer is given in the right column. Instruct the patient to answer how it currently describes their feelings.

A	**I feel tense or 'wound up':**	
	Most of the time	3
	A lot of the time	2
	From time to time, occasionally	1
	Not at all	0

D	**I still enjoy the things I used to enjoy:**	
	Definitely as much	0
	Not quite so much	1
	Only a little	2
	Hardly at all	3

A	**I get a sort of frightened feeling as if something awful is about to happen:**	
	Very definitely and quite badly	3
	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0

D	**I can laugh and see the funny side of things:**	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2
	Not at all	3

A	**Worrying thoughts go through my mind:**	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not too often	1
	Only occasionally	0

D	**I feel cheerful:**	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0

A	**I can sit at ease and feel relaxed:**	
	Definitely	0
	Usually	1
	Not Often	2
	Not at all	3

D	**I feel as if I am slowed down:**	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0

A	**I get a sort of frightened feeling like 'butterflies' in the stomach:**	
	Not at all	0
	Occasionally	1
	Quite Often	2
	Very Often	3

D	**I have lost interest in my appearance:**	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care as ever	0

A	**I feel restless as I have to be on the move:**	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0

D	**I look forward with enjoyment to things:**	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3

A	**I get sudden feelings of panic:**	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0

D	**I can enjoy a good book or radio or TV program:**	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

	Scoring (add the As = Anxiety. Add the Ds = Depression). The norms below will give you an idea of the level of Anxiety and Depression.	
	0-7 = Normal	
	8-10 = Borderline abnormal	
	11-21 = Abnormal	

Reference: *Zigmond and Snaith (1983)*

Figure iii.6: Hospital Anxiety and Depression (HAD) Scale

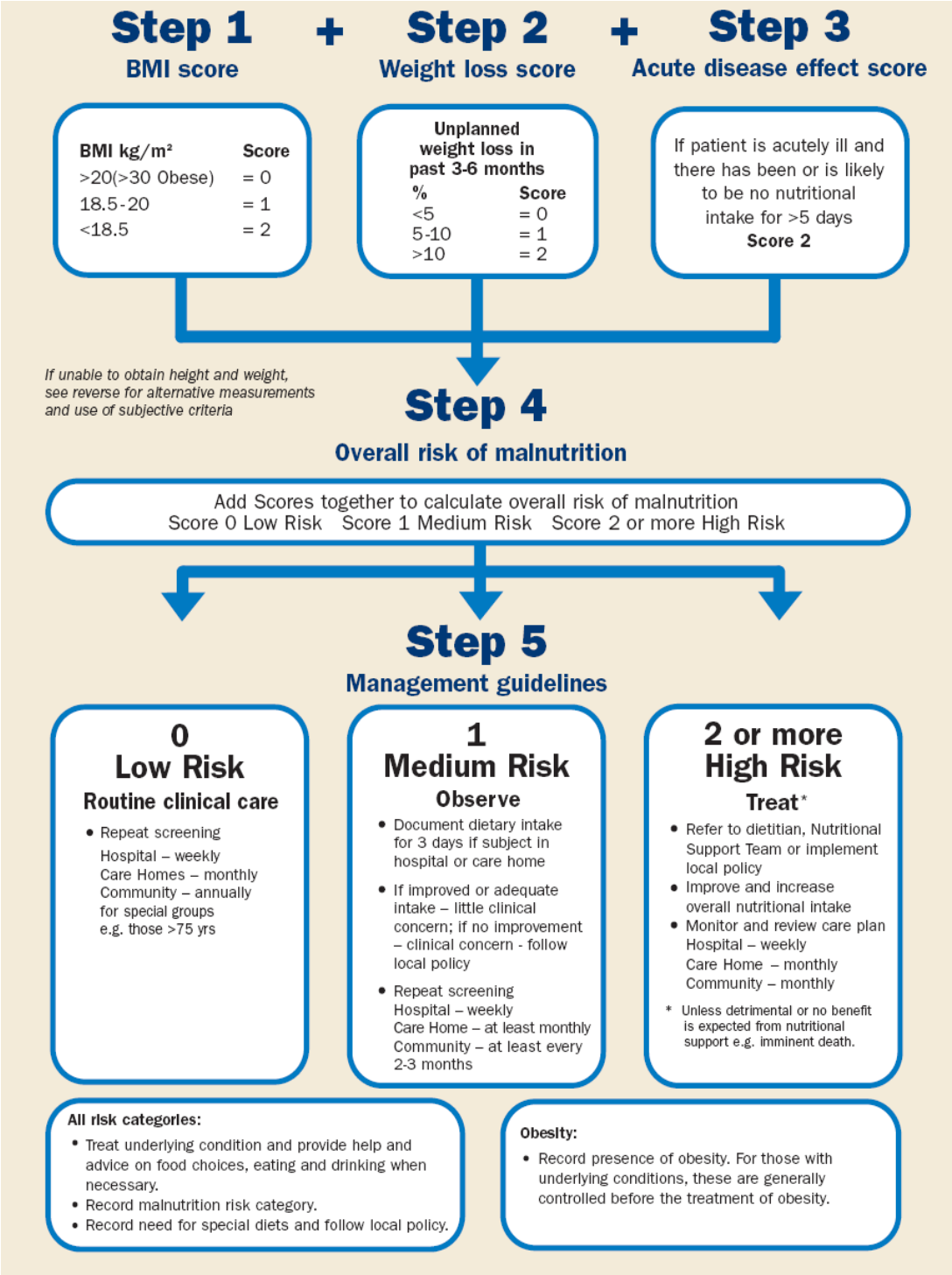


Figure iii.7: MUST scoring system (reproduced from Todorovic *et al.*, 2003)

APPENDIX 4: ESTIMATING NUTRITIONAL REQUIREMENTS

Estimating nutritional requirements for adults

Objectives

- To provide guidelines on the nutritional requirements for adults requiring enteral or parenteral nutrition

Estimation of energy requirements for adults

1. Determine approximate basal metabolic rate (BMR)

2. Adjust for stress or weight gain/ loss:
   If patient is stressed, add a factor that estimates the increased energy requirements due to disease process

   Or, if an increase or decrease in energy stores is required, add or subtract 400 – 1000kcal/day.

3. Add a combined factor for activity and diet-induced thermogenesis (DIT).

Bed bound immobile	+10%
Bed bound mobile/ sitting	+15–20%
Mobile on ward	+25%
Mobile community patients consider using PAL	

Table — Equations for estimating basal metabolic rate (Schofield)

Females (kcal/day)		Males (kcal/day)	
10-17 years	13.4W + 692	10-17 years	17.7W + 657
18-29 years	14.8W + 487	18-29 years	15.1W + 692
30-59 years	8.3W + 846	30-59 years	11.5W + 873
Females over 60 yrs (kcal/day)		**Males over 60 yrs (kcal/day)**	
60 – 74 years	9.2W + 687	60 – 74 years	11.9W + 700
75 years +	9.8W + 624	75 years +	8.3W + 820

W = weight in kg
Conversion 1kcal = 4.184kJ

Figure iv.1: Estimation of nutritional requirements for adults using the Schofield method (adapted from Todorovic and Micklewright, 2004)

APPENDIX 5: CONSTITUENTS OF FEEDS & MULTIVITAMINS

Nutritional Information	unit	250ml can, 500ml & 1l RTH formulation per 100ml	1.5l RTH formulation per 100ml
Energy	kJ	424	424
	kcal	101	101
Protein	g	4.00	4.00
Carbohydrate	g	13.6	13.6
of which sugars	g	0.63	0.70
Fat	g	3.40	3.40
of which saturates	g	0.83	0.90
Fibre	g	0	0
Vitamins	**unit**	**per 100ml**	**per 100ml**
Vitamin A (RE)	µg	108	108
Vitamin D	µg	0.73	0.73
Vitamin E	mg	2.14	2.14
Vitamin C	mg	10.0	10.0
Thiamin (vitamin B1)	mg	0.16	0.16
Riboflavin (vitamin B2)	mg	0.18	0.18
Niacin	mg	1.70	1.70
Vitamin B6	mg	0.22	0.22
Folacin (folic acid)	µg	23.0	23.0
Vitamin B12	µg	0.34	0.34
Biotin	µg	4.60	4.60
Pantothenic acid	mg	0.78	0.78
Vitamin K	µg	5.20	5.20
Minerals	**unit**	**per 100ml**	**per 100ml**
Sodium	mg (mmol)	88.0 (3.83)	88.0 (3.83)
Calcium	mg	68.0	68.0
Phosphorus	mg	68.0	68.0
Iron	mg	1.40	1.40
Magnesium	mg	20.0	20.0
Zinc	mg	1.30	1.30
Iodine	µg	11.0	11.0
Potassium	mg (mmol)	148 (3.79)	148 (3.79)
Chloride	mg (mmol)	136 (3.83)	136 (3.83)
Copper	µg	170	170
Manganese	mg	0.38	0.38
Selenium	µg	6.00	6.00
Chromium	µg	6.50	6.50
Molybdenum	µg	12.0	12.0
Choline	mg	56.0	56.0

Osmolality	288mOsm/kg H_2O
Osmolarity	244mOsm/litre
Water	84.9ml/100ml
Renal solute load	342mOsm/litre

List Nos.
250ml can: E711024
500ml Ready-To-Hang container: E711015
1000ml Ready-To-Hang container: E71100812
1500ml Ready-To-Hang container: W040006

Figure v.1: Osmolite (Abbott Laboratories Ltd., Kent, UK) 1kcal/ml enteral feed.

Fresubin® original

PRESENTATION
Nutritionally complete, 1kcal/ml, tube feed. Fibre free.
Free from gluten and clinically lactose free.

		per 100ml
Energy	kcal(kJ)	100(420)
Protein (15% energy)	g	3.8
Carbohydrate (55% energy)	g	13.8
of which sugars	g	1
of which lactose	g	≤0.02
Fat (30% energy)	g	3.4
of which saturated fatty acids	g	0.3
of which monounsaturated fatty acids	g	2.1
of which polyunsaturated fatty acids	g	1
of which EPA and DHA	g	0.03
Fibre	g	0
Water	ml	84
Osmolarity	mosmol/l	250
Osmolality	mosmol/kg H_2O	300
Sodium	mg (mmol)	75 (3.3)
Potassium	mg (mmol)	125 (3.2)
Chloride	mg (mmol)	115 (3.3)
Calcium	mg	80
Phosphorus	mg	63
Magnesium	mg	25
Iron	mg	1.33
Zinc	mg	1.2
Copper	mg	0.13
Manganese	mg	0.27
Iodide	µg	13.3
Chromium	µg	6.7
Molybdenum	µg	10
Fluoride	mg	0.13
Selenium	µg	6.7
Vitamin A	µgRE	70
Beta-carotene	mg	0.13
Vitamin D	µg	1
Vitamin E	mgαTE	1.33
Vitamin K	µg	6.67
Vitamin B1	mg	0.13
Vitamin B2	mg	0.17
Niacin	mg	1.6
Vitamin B6	mg	0.16
Vitamin B12	µg	0.27
Pantothenic Acid	mg	0.47
Biotin	µg	5
Folic Acid	µg	26.7
Vitamin C	mg	6.67
Choline	mg	36.7

1500ml of Fresubin® original meets the average adult recommended daily requirements for vitamins, minerals and trace elements.

Figure v.2: Fresubin Original® 1 kcal ml^{-1} polymeric feed (Fresenius Kabi Ltd, Cheshire, United Kingdom)

Kabiven® Emulsion for infusion

Active Substances: Qualitative and Quantitative Composition:

Active Substances	2566 ml	2053 ml	1540 ml	1026 ml
Purified soybean oil	100 g	80 g	60 g	40 g
Glucose monohydrate	275 g	220 g	165 g	110 g
Corresponding to Glucose (anhydrous)	250 g	200 g	150 g	100 g
Alanine	12.0 g	9.6 g	7.2 g	4.8 g
Arginine	8.5 g	6.8 g	5.1g	3.4 g
Aspartic acid	2.6 g	2.0 g	1.5 g	1.0 g
Glutamic acid	4.2 g	3.4 g	2.5 g	1.7 g
Glycine	5.9 g	4.7 g	3.6 g	2.4 g
Histidine	5.1 g	4.1 g	3.1 g	2.0 g
Isoleucine	4.2 g	3.4 g	2.5 g	1.7 g
Leucine	5.9 g	4.7 g	3.6 g	2.4 g
Lysine hydrochloride	8.5 g	6.8 g	5.1 g	3.4 g
Corresponding to Lysine	6.8 g	5.4 g	4.1 g	2.7 g
Methionine	4.2 g	3.4 g	2.5 g	1.7 g
Phenylalanine	5.9 g	4.7 g	3.6 g	2.4 g
Proline	5.1 g	4.1 g	3.1 g	2.0 g
Serine	3.4 g	2.7 g	2.0 g	1.4 g
Threonine	4.2 g	3.4 g	2.5 g	1.7 g
Tryptophan	1.4 g	1.1 g	0.86 g	0.57 g
Tyrosine	0.17 g	0.14 g	0.10 g	0.07 g
Valine	5.5 g	4.4 g	3.3 g	2.2 g
Calcium chloride.$2H_2O$	0.74 g	0.59 g	0.44 g	0.29 g
Corresponding to Calcium chloride	0.56 g	0.44 g	0.33 g	0.22 g
Sodium glycerophosphate (anhydrous)	3.8 g	3.0 g	2.3 g	1.5 g
Magnesium sulphate.$7H_2O$	2.5 g	2.0 g	1.5 g	0.99 g
Corresponding to Magnesium sulphate	1.2 g	0.96 g	0.72 g	0.48 g
Potassium chloride	4.5 g	3.6 g	2.7 g	1.8 g
Sodium acetate.$3H_20$	6.1 g	4.9 g	3.7 g	2.5 g
Corresponding to Sodium acetate	3.7 g	2.9 g	2.2 g	1.5 g

Figure v.3: Composition of Kabiven® 14 (Fresenius Kabi Ltd, Cheshire, UK), a 0.9 kcal ml^{-1} parenteral feed represented by the 2566ml bag above.

Kabiven® Peripheral Emulsion for infusion

Active Substances: Qualitative and Quantitative Composition:

Active Substances	2400 ml	1920 ml	1440 ml
Purified soybean oil	85g	68g	51g
Glucose monohydrate	178g	143g	107g
Corresponding to Glucose (anhydrous)	162g	130g	97g
Alanine	8.0g	6.4g	4.8g
Arginine	5.6g	4.5g	3.4g
Aspartic acid	1.7g	1.4g	1.0g
Glutamic acid	2.8g	2.2g	1.7g
Glycine	4.0g	3.2g	2.4g
Histidine	3.4g	2.7g	2.0g
Isoleucine	2.8g	2.2g	1.7g
Leucine	4.0g	3.2g	2.4g
Lysine hydrochloride	5.6g	4.5g	3.4g
Corresponding to Lysine	4.5g	3.6g	2.7g
Methionine	2.8g	2.2g	1.7g
Phenylalanine	4.0g	3.2g	2.4g
Proline	3.4g	2.7g	2.0g
Serine	2.2g	1.8g	1.4g
Threonine	2.8g	2.2g	1.7g
Tryptophan	0.95g	0.76g	0.57g
Tyrosine	0.12g	0.092g	0.069g
Valine	3.6g	2.9g	2.2g
Calcium chloride.$2H_2O$	0.49g	0.39g	0.29g
Corresponding to Calcium Chloride	0.37g	0.30g	0.22g
Sodium Glycerophosphate (anhydrous)	2.5g	2.0g	1.5g
Magnesium Sulphate.$7H_2O$	1.6g	1.3g	0.99g
Corresponding to Magnesium Sulphate	0.80g	0.64g	0.48g
Potassium Chloride	3.0g	2.4g	1.8g
Sodium Acetate.$3H_20$	4.1g	3.3g	2.5g
Corresponding to Sodium Acetate	2.4g	2.0g	1.5g

Figure v.4: Composition of Kabiven® peripheral 9 (Fresenius Kabi Ltd, Cheshire, UK), a 0.7 kcal ml^{-1} parenteral feed represented by the 2400ml bag above.

Each capsule of Forceval® contains:

Vitamin A (as β-Carotene) HSE 2,500.0 iu
Vitamin D2 (Ergocalciferol) HSE 400.0 iu
Vitamin B1 (Thiamine) USP 1.2 mg
Vitamin B2 (Riboflavin) BP 1.6 mg
Vitamin B6 (Pyridoxine) BP 2.0 mg
Vitamin B12 (Cyanocobalamin) PhEur 3.0 mcg
Vitamin C (Ascorbic Acid) BP 60.0 mg
Vitamin E (dl-α-Tocopheryl Acetate) USP 10.0 mg
d-Biotin (Vitamin H) FCC 100.0 mcg
Nicotinamide (Vitamin B3) BP 18.0 mg
Pantothenic Acid (Vitamin B5) USP 4.0 mg
Folic Acid (Vitamin B Complex) BP 400.0 mcg
Calcium FCC 100.0 mg
Iron BP 12.0 mg
Copper HSE 2.0 mg
Phosphorus HSE 77.0 mg
Magnesium BP 30.0 mg
Potassium HSE 4.0 mg
Zinc HSE 15.0 mg
Iodine BP 140.0 mcg
Manganese HSE 3.0 mg
Selenium BP 50.0 mcg
Chromium HSE 200.0 mcg
Molybdenum HSE 250.0 mcg

Figure v.5: Composition of Forceval® capsules (Alliance Pharmaceuticals**,** Chippenham, UK; formerly provided by Unigreg Ltd.)

REFERENCES

Abou-Assi SG, Khurana V and Schubert ML. (2005) Gastric and Postpyloric Total Enteral Nutrition. *Curr Treat Options Gastroenterol*. 8(2): 145-152.

Ackland G, Grocott MP and Mythen MG. (2000) Understanding gastrointestinal perfusion in critical care: so near, and yet so far. *Crit Care.* 4(5): 269-281.

Adler EM. (2005) Focus issue: going for the gut. *Sci STKE.* 277: eg4.

Ahmed W, Levy H, Kudsk KA, *et al.* (1999) The rates of spontaneous transpyloric passage of three enteral feeding tubes. *Nutr Clin Pract.* 14: 107-110.

Aldawood A, Arabi Y and Dabbagh O. (2006) Association of obesity with increased mortality in the critically ill patient. *Anaesth Intensive Care*. 34(5): 629-633.

Alican I and Kubes P. (1996) A critical role for nitric oxide in intestinal barrier function and dysfunction. *Am J Physiol.* 270: G225–237.

Ambrose NS, Johnson M, Burdon DW, *et al.* (1984) Incidence of pathogenic bacteria from mesenteric lymph nodes and ileal serosa during Crohn's disease surgery. *Br J Surg.* 71: 623-625.

Ammori BJ, Leeder PC, King RF, *et al.* (1999) Early increase in intestinal permeability in patients with severe acute pancreatitis: correlation with endotoxemia, organ failure, and mortality. J Gastrointest Surg. 3(3): 252-262.

Anderson AD, McNaught CE, MacFie J, *et al*. (2003) Randomized clinical trial of multimodal optimization and standard perioperative surgical care. *Br J Surg*. 90: 1497-1504.

Anderson AD, Jain PK, Fleming S, *et al*. (2004) Evaluation of a triple sugar test of colonic permeability in humans. *Acta Physiol Scand*. 182(2): 171-177.

Anderson AD, Poon P, Greenway GM, *et al*. (2005) A simple method for the analysis of urinary sucralose for use in tests of intestinal permeability. *Ann Clin Biochem*. 42(Pt 3): 224-226.

Apostolakos MJ. (1995) The gastrointestinal tract and critical illness. Is more perfusion better? *Chest*. 108(6): 1491-1492.

Artinian V, Krayem H and DiGiovine B. (2006) Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. *Chest*. 129(4): 960-967.

Asfar P, Hauser B, Radermacher P, *et al.* (2006) Catecholamines and vasopressin during critical illness. *Crit Care Clin.* 22(1): 131-149, vii-viii.

ASPEN Board of Directors and the Clinical Guidelines Task Force. (2002) Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr.* 26(1 Suppl): 1SA-138SA.

Bai M, Jiang Z and Liu Y. (1996) Glutamine dipeptide attenuate mucosal atrophic changes and preservation of gut barrier function following 5-FU intervention. *Zhonghua Wai Ke Za Zhi*. 34(6): 370-373.

Baig MK and Wexner SD. (2004) Postoperative ileus: a review. *Dis Colon Rectum.* 47: 516-526.

Baines M and Shenkin A. (2002) Use of antioxidants in surgery: a measure to reduce postoperative complications. *Curr Opin Clin Nutr Metab Care*. 5(6): 665-670.

Baker JP, Detsky AS, Wesson DE, *et al.* (1982) Nutritional assessment: a comparison of clinical judgement and objective measurements. *N Engl J Med*. 306(16): 969-972.

Baker LW and Dudley HAF. (1961) Auscultation of the abdomen in surgical patients. *Lancet.* 2: 517-519.

Barber AE, Jones WG 2nd, Minei JP, *et al.* (1991) Bacterial overgrowth and intestinal atrophy in the etiology of gut barrier failure in the rat. Am J Surg. 161(2): 300-304.

Basse L, Raskov HH, Hjort Jakobsen D, *et al.* (2002) Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition. *Br J Surg.* 89: 446-453.

Bastien O, Piriou V, Aouifi A, *et al.* (1998) Effects of dopexamine on blood flow in multiple splanchnic sites measured by laser Doppler velocimetry in rabbits undergoing cardiopulmonary bypass. *Br J Anaesth*. 82: 104-109.

Baumgart DC and Dignass AU. (2002) Intestinal barrier function. *Curr Opin Clin Nutr Metab Care.* 5(6): 685-694.

Beale RJ, Sherry T, Lei K, *et al.* (2008) Early enteral supplementation with key pharmaconutrients improves Sequential Organ Failure Assessment score in critically ill patients with sepsis: outcome of a randomized, controlled, double-blind trial. *Crit Care Med*. 36(1): 131-144.

Beattie AH, Prach AT, Baxter JP, *et al.* (2000) A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. *Gut.* 46(6): 813–818.

Beier-Holgersen R and Boesby S. (1998) Effect of early postoperative enteral nutrition on postoperative infections. *Ugeskr Laeger*. 160: 3223-3226.

Beloosesky Y, Grinblat J, Weiss A, *et al*. (2003) Electrolyte disorders following oral sodium phosphate administration for bowel cleansing in elderly patients. *Arch Intern Med*. 163: 803-808.

Bengmark S. (1996) Econutrition and health maintenance: a new concept to prevent inflammation, ulceration and sepsis. *Clin Nutr*. 15: 1–10.

Bengmark S. (2000) Prospects for new and rediscovered therapies: probiotics and phage. In: *Fighting infection in the 21st century*. Andrew PW, Oyston P, Smith GL, Stewart-Tull DE, eds. pp. 97-132. Blackwell Science Ltd.

Berg RD and Garlington AW. (1979). Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in the gnotobiotic mouse model. Infect Immun. 23(2): 403-411.

Bernik TR, Friedman SG, Ochani M, *et al*. (2002) Pharmacological stimulation of the cholinergic anti-inflammatory pathway. *J Exp Med*. 195(6): 781-788.

Bertolini G, Iapichino G, Radrizzani D, *et al*. (2003) Early enteral immunonutrition in patients with severe sepsis: results of an interim analysis of a randomized multicentre clinical trial. *Int Care Med*. 29(5): 834-840.

Binnekade JM, Tepaske R, Bruynzeel P, *et al*. (2005) Daily enteral feeding practice on the ICU: attainment of goals and interfering factors. *Crit Care*. 9(3): R218-225.

Bone RC, Balk RA and Cerra FB. (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 101: 1644-1655.

Boulton-Jones JR, Lewis J, Jobling JC, T *et al*. (2004) Experience of post-pyloric feeding in seriously ill patients in clinical practice. *Clin Nutr*. 23(1): 35-41.

Bowler RH, Cerra FB, Bershadsky B, *et al*. (1995) Early enteral administration of a formula (Impact®) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: Results of a multicenter, prospective, randomized, clinical trial. *Crit Care Med.* 26: 1164-1172.

Brady M, Kinn S and Stuart P. (2003) Preoperative fasting for adults to prevent perioperative complications. *Cochrane Database Syst Rev.* 2003;(4): CD004423.

Bragg LE, Thompson JS, and Rikkers LF. (1991) Influence of nutrient delivery on gut structure and function. *Nutrition.* 7(4): 237-243.

Brundin T, Branstrom R and Wahren J. (1996) Effects of oral vs. i.v. glucose administration on splanchnic and extrasplanchnic O2 uptake and blood flow. *Am J Physiol*. 271(3 Pt 1): E496-504.

Burke DJ, Alverdy JC, Aoys E, *et al*. (1989) Glutamine-supplemented total parenteral nutrition improves gut immune function. *Arch Surg.* 124: 1396–1399.

Byers RJ, Eddleston JM, Pearson RC, *et al*. (1999) Dopexamine reduces the incidence of acute inflammation in the gut mucosa after abdominal surgery in high-risk patients. *Crit Care Med*. 27 (9): 1787-1793.

Carlson GL, Gray P, Arnold J, *et al.* (1994) Thermogenic, hormonal, and metabolic effects of a TPN mixture. Influence of glucose and amino acids. *Am J Physiol*. 266(6 Pt 1): E845-851.

Carrico CJ, Meakins JL, Marshall JC, *et al.* (1986) Multiple-organ-failure syndrome. *Arch Surg.* 121(2): 196-208.

Carver JD. (1999) Dietary nucleotides: effects on the immune and gastrointestinal systems. *Acta Paediatr Suppl.* 88: 83–88.

Chahal H, Anderson ADG, Gatt M, *et al.* An audit of optimal nutrition. *Clin Nutr.* 23: 909-928.

Chandra RK and Gupta SP. (1991) Increased bacterial adherence to respiratory and buccal epithelial cells in protein-energy malnutrition. *Immunol Infect Dis.* 1: 55-57.

Cheatham ML, Chapman WC, Key SP, *et al.* (1995) A meta-analysis of selective *versus* routine nasogastric decompression after elective laparotomy. *Ann Surg*. 221: 469-476.

Clark JA and Coopersmith CM. (2007) Intestinal crosstalk: a new paradigm for understanding the gut as the "motor" of critical illness. *Shock.* 28(4): 384-393.

Clarkson JP and Elmes ME. (1987) Correlation of plasma zinc and ileal enterocyte zinc in man. *Ann Nutr Metab*. 31: 259–264.

Cohen DB, Magnotti LJ, Lu Q, *et al.* (2004). Pancreatic duct ligation reduces lung injury following trauma and hemorrhagic shock. *Ann Surg.* 240(5): 885-891.

Copeland GP, Jones D and Walters M. (1991) POSSUM: a scoring system for surgical patients. *Br J Surg.* 78: 355-360.

Creteur J, De Backer D and Vincent JL. (1999) A dobutamine test can disclose hepatosplanchnic hypoperfusion in septic patients. *Am J Respir Crit Care Med.* 160: 839-845.

Daly J, Reynolds J, Thom A. (1988) Immune and metabolic effects of arginine in the surgical patient. *Ann Surg*. 208: 512–523.

Daly JM, Lieberman MD, Goldfine J, *et al.* (1992) Enteral nutrition with supplemental arginine, RNA, and omega-3 fatty acids in patients after operation: immunologic, metabolic, and clinical outcome. *Surgery.* 112: 56–67.

Davies AR, Froomes PR, French CJ, *et al.* (2002) Randomized comparison of nasojejunal and nasogastric feeding in critically ill patients. *Crit Care Med*. 30(3): 586-590.

Dawson J. (2007) Nasogastric tube incidents and the use of the 'whoosh test'. *Crit Care.* 11(4): 419.

Deitch EA. (1989) Simple intestinal obstruction causes bacterial translocation in man. *Arch Surg*. 124: 699-701.

Deitch EA, Winterton J and Berg R. (1987) Effect of starvation, malnutrition, and trauma on the gastrointestinal tract flora and bacterial translocation. *Arch Surg.* 122(9): 1019-1024.

Deitch EA, Winterton J, Li M, *et al. (*1987) The gut as portal of entry for bacteremia: role of protein malnutrition. *Ann Surg.* 205: 681-692.

Deitch EA. (1990) Intestinal permeability is increased in burn patients shortly after injury. *Surgery*. 107(4): 411-416.

Deitch EA, Sittig K, Li M, *et al.* (1990[a]) Obstructive jaundice promotes bacterial translocation from the gut. Am J Surg. 159(1): 79-84.

Deitch EA, Ma JA, Ma L, *et al.* (1990 [b]) Protein malnutrition predisposes to inflammatory induced gut-origin septic states. *Ann Surg.* 211: 560-568.

Deitch EA. (1993). Nutrition and the gut mucosal barrier. *Curr Opin Gen Surg.* 85-91.

Deitch EA, Xu D, Naruhn MB, *et al.* (1995) Elemental diet and IV-TPN-induced bacterial translocation is associated with loss of intestinal mucosal barrier function against bacteria. *Ann Surg.* 221(3): 299-307.

Deitch EA. (2001) Role of the gut lymphatic system in multiple organ failure. *Curr Opin Crit Care.* 7(2): 92-98.

Deitch EA. (2002) Bacterial translocation or lymphatic drainage of toxic products from the gut: What is important in human beings? *Surgery.* 131: 241-244.

Deitch EA, Xu D and Kaise VL. (2006) Role of the gut in the development of injury- and shock induced SIRS and MODS: the gut-lymph hypothesis, a review. *Front Biosci.* 11: 520-528.

Delaney CP, Fazio VW, Senagore AJ, *et al.* (2001) 'Fast track' postoperative management protocol for patients with high co-morbidity undergoing complex abdominal and pelvic colorectal surgery. *Br J Surg*. 88: 1533-1538.

de Madaria E, Martinez J, Lozano B, *et al.* (2005) Detection and identification of bacterial DNA in serum from patients with acute pancreatitis. *Gut.* 54(9): 1293-1297.

Desborough JP. (2000) The stress response to trauma and surgery. *Br J Anaesth.* 85(1): 109-117.

DeWitt RC and Kudsk KA. (1999) The gut's role in metabolism, mucosal barrier function, and gut immunology. *Infect Dis Clin North Am.* 13(2): 465-481.

Díaz de Liaño A, Yárnoz C, Artieda C, *et al.* (2005) Enteral nutrition with needle catheter jejunostomy in esophageal anastomosis. Complications of the technique. *Cir Esp*. 77(5): 263-266.

DiFronzo LA, Yamin N, Patel K, *et al.* (2003) Benefits of early feeding and early hospital discharge in elderly patients undergoing open colon resection. *J Am Coll Surg*. 197: 747-752.

Ding LA and Li JS. (2003) Gut in diseases: physiological elements and their clinical significance. *World J Gastroenterol.* 9(11): 2385-2389.

Disbrow EA, Bennett HL and Owings JT. (1993) Effect of preoperative suggestion on postoperative gastrointestinal motility. *West J Med.* 158: 488-492.

Dive A, Moulart M, Jonard P, *et al.* (1994 [a]) Gastroduodenal motility in mechanically ventilated critically ill patients: a manometric study. *Crit Care Med*. 22(3): 441-447.

Dive A, Miesse C, Jamart J, *et al.* (1994 [b]) Duodenal motor response to continuous enteral feeding is impaired in mechanically ventilated critically ill patients. *Clin Nutr*. 13(5): 302-306.

Doganay M, Kama NA, Yazgan A, *et al.* (1997) The effects of vagotomy on bacterial translocation: an experimental study. *J Surg Res.* 71(2): 166-171.

Dominioni L, Rovera F, Pericelli A, *et al.* (2003) The rationale of early enteral nutrition. *Acta Biomed.* 74 Suppl 2: 41-44.

Donati D, Brown SR, Eu KW, *et al.* (2002) Comparison between midline incision and limited right skin crease incision for right-sided colonic cancers. *Tech Coloproctol.* 6: 1-4.

Duggan C, Gannon J and Walker WA. (2002) Protective nutrients and functional foods for the gastrointestinal tract. *Am J Clin Nutr*. 75(5): 789-808.

Egbert LD, Battit GE, Welch CE, *et al.* (1964) Reduction of postoperative pain by encouragement and instruction of patients. *N Engl J Med.* 270: 825-827.

Elia M, Stroud M and. Itobi E. (2006) Impact of oedema on recovery after major abdominal surgery and potential value of multifrequency bioimpedance measurements (*Br J Surg* 2006; 93: 354-361). *Br J Surg.* 93(6): 769-770; author reply 770.

Elpern EH, Killeen K, Talla E, *et al.* (2007) Capnometry and air insufflation for assessing initial placement of gastric tubes. *Am J Crit Care.* 16(6): 544-549.

Ensinger H, Rantala A, Vogt J, *et al.* (1999) Effect of dobutamine on splanchnic carbohydrate metabolism and amino acid balance after cardiac surgery. *Anesthesiology.* 91: 1587-1595.

Fearon KC, Ljungqvist O, Von Meyenfeldt M, *et al.* (2005) Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr.* 24(3): 466-477.

Fine J. (1965). Current status of the problem of traumatic shock. *Surg Gynecol Obstet.* 120: 537-544.

Fleisch AL. (1951) Le metabolisme basal standard et sa determination au moyen du 'metabocalculator'. *Helv Med Acta* 18: 23-44.

Fleming CR and Remington M. (1981) Intestinal failure. In: *Nutrition and the Surgical Patient*, pp. 219–235 (Hill GL, ed.). Churchill Livingstone, New York.

Flexner S. (1895) Peritonitis caused by the invasion of the Micrococcus Lanceolatus from the intestine. *John Hopkins Hosp Bull.* 6: 64-67.

Ford WW. (1900) The bacteriology of healthy organs. *Trans Assoc Am Physicians.* 15: 389-415.

Fong YM, Marano MA, Barber A, *et al.* (1989) Total parenteral nutrition and bowel rest modify the metabolic response to endotoxin in humans. *Ann Surg.* 210(4): 449-456; discussion 456-457.

Fraenkel A. (1891) Ueber peritoneale infection. *Wein Klin Wochenschr.* 121: 265-285.

Frances R, Rodriguez E, Munoz C, *et al.* (2005) Intracellular cytokine expression in peritoneal monocyte/macrophages obtained from patients with cirrhosis and presence of bacterial DNA. *Eur J Gastroenterol Hepatol.* 17(1): 45-51.

Gabriel SA and Ackermann RJ. (2004) Placement of nasoenteral feeding tubes using external magnetic guidance. *JPEN J Parenter Enteral Nutr.* 28: 119-122.

Galban C, Montejo JC, Mesejo A, *et al.* (2000) An immune-enhancing enteral diet reduces mortality rate and episodes of bacteraemia in septic intensive care unit patients. *Crit Care Med.* 28: 643-648.

Ganong WF (2005). Gastrointestinal function. In: *Review of Medical Physiology, 22nd Edition,* pp.467-514. McGraw Hill Companies.

Garrison RN, Fry DE, Berberich S, *et al.* (1982) Enterococcal bacteremia: clinical implications and determinants of death. Ann Surg. 196(1): 43-47.

Garrouste-Orgeas M, Troché G, Azoulay E, *et al.* (2004) Body mass index. An additional prognostic factor in ICU patients. *Intensive Care Med*. 30(3): 437-443.

Garside P, Millington O and Smith KM. (2004) The anatomy of mucosal immune responses. *Ann N Y Acad Sci.* 1029: 9-15.

Gatt M and MacFie J. (2005) Fast-track surgery (*Br J Surg* 2005; 92: 3-4). *Br J Surg.* 92(4): 494.

Gatt M, Anderson AD, Reddy BS, *et al.* (2005) Randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection. *Br J Surg*. 92(11): 1354-1362.

Gatt M, Reddy BS, and MacFie J. (2007) Review article: bacterial translocation in the critically ill - evidence and methods of prevention. *Aliment Pharmacol Ther.* 25(7): 741-57.

Gatt M, MacFie J, McNaughton L, *et al.* (2007) Gut function is an independent indicator of patient outcome: proof of principle. Clin Nutr. 2(Suppl 2): 108.

Geelkerken RH, Lamers CB, Delahunt TA, *et al.* (1998) Duodenal meal stimulation leads to coeliac artery vasoconstriction and superior mesenteric artery vasodilatation: an intra-abdominal ultrasound study. *Ultrasound Med Biol.* 24: 1351–1356.

Gibson GR, Beatty ER, Wang X, *et al.* (1995) Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin. *Gastroenterology.* 108: 975–982.

Ginsberg JM, and Costoff A. (2000) Gastrointestinal physiology. In: *Essentials of Human Physiology (CD-ROM edition)*. Section 6. Nosek T.M. (Ed). Gold Standard Multimedia Inc.

Grantcharov TP and Rosenberg J. (2001) Vertical compared with transverse incisions in abdominal surgery. *Eur J Surg*. 167: 260-267.

Greif R, Laciny S, Rapf B, *et al*. (1999) Supplemental oxygen reduces the incidence of postoperative nausea and vomiting. *Anesthesiology*. 91: 1246-1252.

Greif R, Akca O, Horn EP, *et al*. (2000) Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med*. 342: 161-167.

Gruys E, Toussaint MJ, Niewold TA, *et al*. (2005) Acute phase reaction and acute phase proteins. *J Zhejiang Univ Sci B*. 6(11): 1045-1056.

Guenaga KF, Matos D, Castro AA, *et al*. (2003) Mechanical bowel preparation for elective colorectal surgery. *Cochrane Database Syst Rev* 2003; 2: CD001544.

Harris JA and Benedict FG. (1919) A biometric study of basal metabolism in man. In: *Publication no. 279.* Carnegie Institute of Washington, Washington D.C.

Hasko G, Szabo C, Nemeth ZH, *et al*. (1998) Modulation by dantrolene of endotoxin-induced interleukin-10, tumour necrosis factor-alpha and nitric oxide production in vivo and in vitro. *Br J Pharmacol.* 124(6): 1099-1106.

Hathaway D. (1986) Effects of preoperative instruction on postoperative outcomes: a meta-analysis. Nurs Res. 35: 269-274.

Hausel J, Nygren J, Thorell A, *et al*. (2005) Randomized clinical trial of the effects of oral preoperative carbohydrates on postoperative nausea and vomiting after laparoscopic cholecystectomy. *Br J Surg*. 92: 415-421.

Hernandez Oliveros F, Zou Y, Lopez G, *et al*. (2004) Critical assessment of the methods used for detection of bacterial translocation. *Pediatr Surg Int.* 20(4): 267-270.

Henriksen MG. (2000) *Aspects of perioperative treatment in abdominal surgery*. PhD Thesis, University of Aarhus, Denmark.

Hernandez-Socorro CR, Marin J, Ruiz-Santana S, *et al.* (1996) Bedside sonographic-guided *versus* blind nasoenteric feeding tube placement in critically ill patients. *Crit Care Med*. 24: 1690-1694.

Heyland DK, Drover JW, MacDonald S, *et al.* (2001[a]) Effect of postpyloric feeding on gastroesophageal regurgitation and pulmonary microaspiration: results of a randomized controlled trial. *Crit Care Med*. 29(8): 1495-1501.

Heyland DK, Novak F, Drover JW, *et al.* (2001[b]) Should immunonutrition become Routine in critically ill patients? A systematic review of the evidence. *JAMA.* 286: 944-953.

Heyland DK, Novak F, Avenell A, *et al.* (2002) Glutamine supplementation in serious illness: a systematic review of the evidence. *Am J Clin Nutr.* 75(suppl): 416S–417S.

Heyland DK, Dhaliwal R, Drover JW, *et al.* (2003) Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr*. 27(5): 355-373.

Heyland DK, Dhaliwal R, Day A, *et al.* (2004) Validation of the Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients: results of a prospective observational study. *Crit Care Med.* 32(11): 2260-2266.

Heys SD, Walker LG, Smith I, *et al.* (1999) Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer: a meta-analysis of randomized controlled clinical trials. *Ann Surg.* 229: 467-477.

Hillard AE, Wadder JJ, Metzler MH, *et al*. (1995) Fluoroscopically guided nasoenteric feeding tube placement *versus* bedside placement. *South Med J.* 88: 425-428.

Hiltebrand LB, Krejci V and Sigurdsson GH. (2004) Effects of dopamine, dobutamine, and dopexamine on microcirculatory blood flow in the gastrointestinal tract during sepsis and anesthesia. *Anesthesiology*. 100(5): 1188-1197.

Ho KM, Dobb GJ and Webb SA. (2006) A comparison of early gastric and post-pyloric feeding in critically ill patients: a meta-analysis. *Intensive Care Med*. 32(5):639-649.

Hoffmann S, Koller M, Plaul U, *et al*. (2001) Nasogastric tube *versus* gastrostomy tube for gastric decompression in abdominal surgery: a prospective, randomized trial comparing patients' tube-related inconvenience. *Langenbecks Arch Surg.* 386: 402-409.

Holte K, Sharrock NE and Kehlet H. (2002) Pathophysiology and clinical implications of perioperative fluid excess. *Br J Anaesth.* 89(4): 622-632.

Hua TC and Moochhala SM. (2000) Role of nitric oxide in hemorrhagic shock-induced bacterial translocation. *J Surg Res.* 93(2): 247-256.

Iwao T, Toyonaga A, Shigemori H, *et al*. (1996) Echo-Doppler measurements of portal vein and superior mesenteric artery blood flow in humans: Inter- and intra- observer short term reproducibility. *J Gastroenterol Hepatol.* 11: 40-46.

Jacob S, Weizel H, Gordon E, *et al*. (1954) Bacterial action in development of irreversibility to transfusion in haemorrhagic shock in the dog. *Am J Physiol.* 179: 523-540.

Jain PK, McNaught CE, Anderson AD, *et al*. (2004) Influence of synbiotic containing Lactobacillus acidophilus La5, Bifidobacterium lactis Bb 12, Streptococcus thermophilus, Lactobacillus bulgaricus and oligofructose on gut barrier function and sepsis in critically ill patients: a randomised controlled trial. *Clin Nutr.* 23(4): 467-475.

Jeejeebhoy KN. (2001) Total parenteral nutrition: potion or poison. *Am J Clin Nutr.* 74: 160-163.

Jeejeebhoy KN. (2002) Enteral feeding. *Curr Opin Gastroenterol*. 18(2): 209-212.

Jeejeebhoy KN. (2005) The etiology and mechanism of intestinal failure. In: *Intestinal failure and rehabilitation: a clinical guide.* Matarese LE, Steiger E and Seidner DL (Eds.) pp. 25-37. CRC Press, New York.

Johnson CD and Kudsk KA. (1999) Nutrition and intestinal mucosal immunity. *Clin Nutr.* 18(6): 337-344.

Jorba R, Fabregat J, Garcia Borobia F, *et al.* (2000) Small bowel necrosis in association with early post-operative enteral feeding after pancreatic resection. *Surgery*. 128: 111-112.

Jorgensen H, Wetterslev J, Moiniche S, *et al*. (2000) Epidural local anaesthetics *versus* opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. *Cochrane Database Syst Rev.* 2000(4): CD001893.

Kabaroudis A, Papaziogas B, Koutelidakis I, *et al.* (2003) Disruption of the small-intestine mucosal barrier after intestinal occlusion: a study with light and electron microscopy. *J Invest Surg.* 16(1): 23-28.

Kam MH, Seow-Choen F, Peng XH, *et al*. (2004) Minilaparotomy left iliac fossa skin crease incision vs. midline incision for left-sided colorectal cancer. *Tech Coloproctol.* 8: 85-88.

Kan MN, Chang HH, Sheu WF, *et al*. (2003) Estimation of energy requirements for mechanically ventilated, critically ill patients using nutritional status. *Crit Care*. 7(5): R108-R115.

Kane TD, Alexander JW and Johannigman JA. (1998) The detection of microbial DNA in the blood: a sensitive method for diagnosing bacteremia and/or bacterial translocation in surgical patients. *Ann Surg.* 227(1): 1-9.

Kehet H and Wilmore DW. (2002) Multimodal strategies to improve surgical outcome. *Am J Surg.* 183: 630-641.

Kehlet H. (2000) Postoperative ileus. *Gut*. 47(Suppl):iv 85-86.

Kehlet H and Holte K. (2001) Review of postoperative ileus. *Am J Surg.* 182(Suppl): 3S–10S.

Kehlet H and Dahl JB. (2003) Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet*. 362: 1921-1928.

Kehlet H and Wilmore DW. (2005) Fast-track surgery. *Br J Surg.* 92(1): 3-4.

Khan S, Gatt M, Petty D, *et al*. (2008) Intestinal Obstruction After PEG Tube Replacement: Implications to Daily Clinical Practice. *Surg Laparosc Endosc Percutan Tech*. 18(1): 80-81.

Kinney JM, Morgan AP, Domingues FJ, *et al.* (1964) A method for continuous measurement of gas exchange and expired radioactivity in acutely ill patients. *Metabolism.* 13: 205-211.

Kleiber M. (1932) Body size and metabolism. *Hilaardia.* 6: 315-353.

Knaus WA, Draper EA, Wagner DP, *et al.* (1985) APACHE II: a severity of disease classification system. *Crit Care Med*. 13(10): 818-829.

Koike K, Moore EE, Moore FA, *et al.* (1994) Gut ischemia/reperfusion produces lung injury independent of endotoxin. *Crit Care Med.* 22(9): 1438-1444.

Koo SI and Turk DE. (1977) Effect of zinc deficiency on the ultrastructure of the pancreatic acinar cell and intestinal epithelium in the rat. *J Nutr*. 107: 896–908.

Kreger BE, Craven DE, Carling PC, *et al.* (1980). Gram-negative bacteremia. III. Reassessment of etiology, epidemiology and ecology in 612 patients. *Am J Med.* 68(3): 332-343.

Kreymann KG, Berger MM, Deutz NE, *et al.* (2006) ESPEN Guidelines on Enteral Nutrition: Intensive care. *Clin Nutr*. 25(2): 210-223.

Krueger WA, Krueger-Rameck S, Koch S, *et al.* (2004) Assessment of the role of antibiotics and enterococcal virulence factors in a mouse model of extraintestinal translocation. *Crit Care Med.* 32(2): 467-471.

Kucukaydin M, Kocaoglu C, Koksal F, *et al.* (2000) Detection of intestinal bacterial translocation in subclinical ischemia-reperfusion using the polymerase chain reaction technique. *J Pediatr Surg.* 35(1): 41-43.

Kurz A and Sessler DL. (2003) Opiod-induced bowel dysfunction: pathophysiology and potential new therapies. *Drugs.* 63: 649-671.

Kueppers PM, Miller TA, Chen CY, *et al.* (1993) Effect of total parenteral nutrition plus morphine on bacterial translocation in rats. *Ann Surg.* 217(3): 286-292.

Kushner I and Rzewnicki DL. (1994) The Acute Phase Response: General aspects. *Baillieres's Clinical Rheumatology.* 8: 513-530.

Kuzu MA, Kale IT, Col C, *et al.* (1999) Obstructive jaundice promotes bacterial translocation in humans. *Hepatogastroenterology.* 46(28): 2159-2164.

Laffineur G, Lescut D, Vincent P, *et al.* (1992) Bacterial translocation in Crohn disease. *Gastroenterol Clin Biol.* 16(10): 777-781.

Lawlor DK, Inculet RI and Malthaner RA. (1998) Small bowel necrosis associated with jejunal tube feeding. *Can J Surg.* 41: 459-462.

Lescut D, Colombel JF, Vincent P, *et al.* (1990) Bacterial translocation in colorectal cancers. *Gastroenterol Clin Biol.* 14(11): 811-814.

Levenson R, Turner WW *et al.* (1988) Do weighted nasoenteric tubes facilitate transpyloric intubation? *JPEN J Parenter Enteral Nutr.* 12: 135-137.

Lewis SJ, Egger M, Sylvester PA, *et al.* (2001) Early enteral feeding *versus* "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. *Br Med J.* 323(7316): 773–776.

Lillehei RC. (1957) The intestinal factor in irreversible haemorrhagic shock. *Surgery.* 42: 1043-1054.

Lindgren PG, Nordgren SR, Oresland T, *et al.* (2001) Midline or transverse abdominal incision for right-sided colon cancer - a randomized trial. *Colorectal Dis.* 3: 46-50.

Lisbon A. (2003) Dopexamine, dobutamine, and dopamine increase splanchnic blood flow: what is the evidence? *Chest*. 123(5 Suppl): 460S-463S.

Ljungqvist O, Nygren J and Thorell A. (2002) Modulation of post-operative insulin resistance by pre-operative carbohydrate loading. *Proc Nutr Soc.* 61: 329-336.

Llovet JM, Bartoli R, March F, *et al.* (1998) Translocated intestinal bacteria cause spontaneous bacterial peritonitis in cirrhotic rats: molecular epidemiologic evidence. *J Hepatol.* 28(2): 307-313.

Loong TW. (2003) Understanding sensitivity and specificity with the right side of the brain. *BMJ*. 327(7417): 716-719.

Lord L, Weiser-Maimone A, Pulhamus M, *et al.* (1993) Comparison of weighted vs. unweighted enteral feeding tubes for efficacy of transpyloric intubation. *JPEN J Parenter Enteral Nutr.* 17: 271-273.

Lu L and Walker WA. (2001) Pathologic and physiologic interactions of bacteria with the gastrointestinal epithelium. *Am J Clin Nutr*. 73(suppl): 1124S–1130S.

Luiking YC and Deutz NE. (2007) Exogenous arginine in sepsis. *Crit Care Med*. 35(9 Suppl): S557-S563.

Lull RJ, Anderson JH, Telepak RJ, *et al.* (1980) Radionuclide imaging in the assessment of lung injury. *Semin Nucl Med*. 10(3): 302-310.

MacFie J, O'Boyle C, Mitchell CJ, *et al*. (1999) Gut origin of sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora, and septic morbidity. *Gut.* 45(2): 223-228.

MacFie J. (2000) Enteral *versus* parenteral nutrition: the significance of bacterial translocation and gut-barrier function. *Nutrition*. 16(7-8): 606-611.

MacFie J, Reddy BS, Gatt M, *et al*. (2006) Bacterial translocation studied in 927 patients over 13 years. *Br J Surg.* 93(1): 87-93.

Madorin WS, Martin CM and Sibbald WJ. (1999) Dopexamine attenuates flow motion in ileal mucosal arterioles in normotensive sepsis. *Crit Care Med*. 27(2): 394-400.

Magnotti LJ and Deitch EA. (2005) Burns, bacterial translocation, gut barrier function, and failure. *J Burn Care Rehabil.* 26(5): 383-391.

Mangiante G, Colucci G, Gottin L, *et al*. (2001) Effect of probiotic administration on colic anastomosis healing. *Chir Ital.* 53: 39-44.

Marderstein EL, Simmons RL and Ochoa JB. (2004) Patient safety: effect of institutional protocols on adverse events related to feeding tube placement in the critically ill. *J Am Coll Surg.* 199(1): 39-47; discussion 47-50.

Marik P E and Zaloga G P. (2003) Gastric *versus* post-pyloric feeding: a systematic review. *Critical Care*. 7(3): R46-R51.

Marshall JC, Christou NV, and Meakins JL. (1993) The gastrointestinal tract: The undrained abscess of multiple organ failure. *Ann Surg.* 218(2): 111-119.

Maynard ND, Bihari DJ, Dalton RN, *et al*. (1995) Increasing splanchnic blood flow in the critically ill. *Chest.* 108: 1648-1654

McClave SA, Lukan JK, Stefater JA, *et al*. (2005) Poor validity of residual volumes as a marker for risk of aspiration in critically ill patients. *Crit Care Med*. 33(2): 324-330.

McCullough F, Northrop-Clewes C and Thurnham D. (1999) The effect of vitamin A on epithelial integrity. *Proc Nutr Soc.* 58: 289–293.

McGuire W and McEwan P. (2007) Transpyloric *versus* gastric tube feeding for preterm infants. *Cochrane Database Syst Rev*. 2007 Jul 18;(3): CD003487.

McNaught CE, Woodcock NP, Mitchell CJ, *et al*. (2002) Gastric colonisation, intestinal permeability and septic morbidity in acute pancreatitis. *Pancreatology*. 2(5): 463-468.

Meddings J and Gibbons I. (1998) Discrimination of site-specific alterations in gastrointestinal permeability in the rat. *Gastroenterology*. 114: 83-92.

Meehan AG and Kreulen DL. (1992) A capsaicin-sensitive inhibitory reflex from the colon to mesenteric arteries in the guinea-pig. *J Physiol*. 448: 153-159.

Meier-Hellmann A, Bredle DL, Specht M, *et al*. (1999) Dopexamine increases splanchnic blood flow but decreases gastric mucosal pH in severe septic patients treated with dobutamine. *Crit Care Med*. 27(10): 2166-2171.

Mentec H, Dupont H, Bocchetti M, *et al*. (2001) Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications. *Crit Care Med*. 29(10): 1955-1961.

Menzies I. (1984) Transmucosal passage of inert molecules in health and disease. In: *Intestinal absorption and secretion. Falk Symposium 36; Lancaster*. (Skadhauge E, Heintze K, eds.) pp. 527-543. MTP Press Ltd.

Merad F, Hay JM, Fingerhut A, *et al.* (1999) Is prophylactic pelvic drainage useful after elective rectal or anal anastomosis? A multicenter controlled randomized trial. *Surgery*. 125: 529-535.

MHRA. (2004) *MHRA medical device alert for enteral feeding tubes (nasogastric).* London: Medicines and Health Regulatory Agency (MHRA); June 2004, Ref. MDA/2004/026.

Milewski PJ, Gross E, Holbrook I, *et al.* (1980) Parenteral nutrition at home in management of intestinal failure. *Br Med J.* 7;280(6228): 1356-1357.

Molyneux CA, Glyn MC and Ward BJ. (2002) Oxidative stress and cardiac microvascular structure in ischemia and reperfusion: the protective effect of antioxidant vitamins. Microvasc Res. 64(2): 265-277.

Moneta GL, Taylor DC, Helton WS, *et al.* (1988) Duplex ultrasound measurement of intestinal blood flow: Effect of meal composition. *Gastroenterology*. 95: 1294-1301.

Montecalvo MA, Steger KA, Farber HW, *et al.* (1992) Nutritional outcome and pneumonia in critical care patients randomized to gastric *versus* jejunal tube feedings. The Critical Care Research Team. *Crit Care Med*. 20(10): 1377-1387.

Montejo J C, Zarazaga A, Lopez-Martinez J, *et al.* (2003) Immunonutrition in the intensive care unit: a systematic review and consensus statement. *Clinical Nutrition*. 22(3): 221-233.

Moore FA, Moore EE, Poggetti R, *et al.* (1991) Gut bacterial translocation via the portal vein: a clinical perspective with major torso trauma. *J Trauma.* 31(5): 629-636.

Moore FA, Feliciano DV, Andrassy RJ, *et al.* (1992) Early enteral feeding, compared with parenteral, reduces postoperative septic complications. The results of a meta-analysis. *Ann Surg*. 216(2): 172-183.

Morrell G. (2001) Effect of structured preoperative teaching on anxiety levels of patients scheduled for cataract surgery. *Insight* 26: 4-9.

Muller M, Boldt J, Schindler E, *et al.* (1999) Effects of low-dose dopexamine on splanchnic oxygenation during major abdominal surgery. *Crit Care Med*. 27(11): 2389-2393.

Munshi IA, Steingrub JS and Wolpert L. (2000) Small bowel necrosis associated with early post-operative jejunal tube feeding in a trauma patient. *J Trauma.* 49: 163-165.

Mythen MG. (2005) Postoperative gastrointestinal tract dysfunction. *Anesth Analg.* 100: 196-204.

National Collaborating Centre for Acute Care. (2006). *Nutrition support in adults Oral nutrition support, enteral tube feeding and parenteral nutrition*. pp. 1-175. Ref: cg032. National Collaborating Centre for Acute Care, London.

Nazli A, Yang PC, Jury J, *et al.* (2004) Epithelia under metabolic stress perceive commensal bacteria as a threat. *Am J Pathol*. 164(3): 947-957.

Neviere R, Mathieu D, Chagnon JL, *et al.* (1996) The contrasting effects of dobutamine and dopamine on gastric mucosal perfusion in septic patients. *Am J Respir Crit Care Med.* 154: 1684-1688.

Nieuwenhuijzen GA, Deitch EA and Goris RJ. (1996) Infection, the gut and the development of the multiple organ dysfunction syndrome. *Eur J Surg.* 162(4): 259-273.

Nightingale J. (2001) Introduction: Definition and classification of intestinal failure. In: *Intestinal failure*. (Nightingale J ed.). pp. xix-xx. Greenwich Medical Media Ltd., London.

Niinikoski H, Stoll B, Guan X, *et al*. (2004) Onset of small intestinal atrophy is associated with reduced intestinal blood flow in TPN-fed neonatal piglets. *J Nutr.* 134(6): 1467-1474.

Niness KR. (1999) Inulin and oligofructose: what are they? *J Nutr*. 129(suppl): 1402S–1406S.

***NPSA (National Patient Safety Agency): Patient Safety Bulletin 3*. (2007)** London: National Patient Safety Agency.

Nursal TZ, Erdogan B, Noyan T, *et al*. (2007) The effect of metoclopramide on gastric emptying in traumatic brain injury. *J Clin Neurosci.* 14(4): 344-348.

O'Boyle CJ, MacFie J, Mitchell CJ, *et al*. (1998[a]) Microbiology of bacterial translocation in humans. *Gut.* 42: 29-35.

O'Boyle CJ, MacFie J, Dave K, *et al*. (1998[b]) Alterations in intestinal barrier function do not predispose to translocation of enteric bacteria in gastroenterological patients. *Nutrition*. 14(4): 358-362.

O'Dwyer S, Smith R, Hwang T, *et al*. (1989) Maintenance of small bowel mucosa with glutamine-enriched parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 13: 579–585.

Ogata Y, Nishi M, Nakayama H, *et al*. (2003) Role of bile in intestinal barrier function and its inhibitory effect on bacterial translocation in obstructive jaundice in rats. *J Surg Res.* 115(1): 18-23.

O'Keefe SJ, Buchman AL, Fishbein TM, *et al.* (2006) Short bowel syndrome and intestinal failure: consensus definitions and overview. *Clin Gastroenterol Hepatol*. 4(1): 6-10.

Pallant J. (2002) Assumptions of multiple regression. In: *SPSS survival manual*. pp. 136-146. Open University Press, Buckingham.

Parker DR, Carlisle K, Cowan FJ, *et al.* (1995) Postprandial mesenteric blood flow in humans: relationship to endogenous gastrointestinal hormone secretion and energy content of food. *Eur J Gastroenterol Hepatol.* 7: 435–440.

Pastores SM, Katz DP and Kvetan V. (1996) Splanchnic ischemia and gut mucosal injury in sepsis and the multiple organ dysfunction syndrome. *Am J Gastroenterol.* 91(9): 1697-1710.

Peake SL, Moran JL, Ghelani DR, *et al.* (2006) The effect of obesity on 12-month survival following admission to intensive care: a prospective study. *Crit Care Med*. 34(12): 2929-2939.

Perko JM and Just S. (1993) Duplex ultrasonography of superior mesenteric artery: Interobserver variability. *J Ultrasound Med.* 5: 259-263.

Phang JS, Marsh WA, Barlows TG, *et al.* (2004) Determining feeding tube location by gastric and intestinal ph values. *Nutr Clin Pract.* 19: 640-644.

Phang J, Marsh W and Prager R. (2006) Feeding tube placement with the aid of a new electromagnetic transmitter. *JPEN J Parenter Enteral Nutr.* 30(2): S082.

Raff T, Hartmann B and Germann G. (1997) Early intragastric feeding of seriously burned and long-term ventilated patients: a review of 55 patients. *Burns*. 23(1): 19-25.

Rastall RA. (2004) Bacteria in the gut: friends and foes and how to alter the balance. *J Nutr*. 134(8 Suppl): 2022S-2026S.

Ratnaraj J, Kabon B, Talcott MR, *et al.* (2004) Supplemental oxygen and carbon dioxide each increase subcutaneous and intestinal intramural oxygenation. *Anesth Analg.* 99: 207-211.

Ravin HA, Rowley D, Jenkins C, *et al.* (1960). On the absorption of bacterial endotoxin from the gastrointestinal tract of the normal and shocked animal. *J Exp Med.* 112: 783-790.

Rayes N, Seehofer D, Muller AR, *et al.* (2002) Influence of probiotics and fibre on the incidence of bacterial infections following major abdominal surgery - results of a prospective trial. *Z Gastroenterol.* 40: 869-876.

Reddy BS, MacFie J, Gatt M, *et al.* (2007 [a]) Commensal bacteria do translocate across the intestinal barrier in surgical patients. *Clin Nutr.* 26(2): 208-215.

Reddy BS, MacFie J, Gatt M, *et al.* (2007 [b]) Randomized clinical trial of effect of synbiotics, neomycin and mechanical bowel preparation on intestinal barrier function in patients undergoing colectomy. *Br J Surg*. 94(5): 546-554.

Rees RG, Payne-James JJ and Silk DC. (1988) Spontaneous transpyloric passage and performance of 'fine bore' polyurethane feeding tubes: A controlled clinical trial. *JPEN J Parenter Enteral Nutr.* 12: 469-472.

Reid C. (2006) Frequency of under- and overfeeding in mechanically ventilated ICU patients: causes and possible consequences. *J Hum Nutr Diet*. 19(1): 13-22.

Reissman P, Teoh TA, Cohen SM, *et al.* (1995) Is early oral feeding safe after elective colorectal surgery? A prospective randomized trial. *Ann Surg.* 222: 73-77.

Reynolds JV, Murchan P, Leonard N, *et al*. (1996) Gut barrier failure in experimental obstructive jaundice. *J Surg Res.* 62(1): 11-16.

Rhoney DH, Parker D Jr, Formea CM, *et al*. (2002) Tolerability of bolus *versus* continuous gastric feeding in brain-injured patients. *Neurol Res.* 24: 613-620.

Ritz MA, Fraser R, Tam W, *et al*. (2000) Impacts and patterns of disturbed gastrointestinal function in critically ill patients. *Am J Gastroenterol*. 95: 3044-3052.

Rives DA, LeRoy JL, Hawkins ML, *et al*. (1989) Endoscopically assisted nasojejunal feeding tube placement. *Am Surgeon*. 55: 88-91.

Robertson JD and Reid DD. (1952) Standards for the basal metabolism of normal people in Britain. *Lancet.* 1(6715): 940-943.

Rombeau JL, and Takala J. (1997). Gut dysfunction in critical illness. *Clin Nutr*. 16(2): 57-60.

Rothnie NG, Harper RA and Catchpole BN. (1963) Early postoperative gastrointestinal activity. *Lancet*. July 13;2: 64-77.

Roy SK, Behrens RH, Haider R, *et al*. (1992) Impact of zinc supplementation on intestinal permeability in Bangladeshi children with acute diarrhoea and persistent diarrhoea syndrome. *J Pediatr Gastroenterol Nutr.* 15: 289–296.

Ruokonen E, Takala J, Kari A, *et al*. (1993) Regional blood flow and oxygen transport in septic shock. *Crit Care Med.* 21: 1296-1303.

Saadia R, Schein M, MacFarlane C, *et al*. (1990) Gut barrier function and the surgeon. *Br J Surg.* 77(5): 487-492.

Saeed RW, Varma S, Peng-Nemeroff T, *et al*. (2005) Cholinergic stimulation blocks endothelial cell activation and leukocyte recruitment during inflammation. *J Exp Med.* 201(7): 1113-1123.

Sagar PM, MacFie J, Sedman P, *et al*. (1995) Intestinal Obstruction promotes gut translocation of bacteria. *Dis Colon Rectum.* 38: 680-684.

Sakrak O, Akpinar M, Bedirli A, *et al*. (2003) Short and long-term effects of bacterial translocation due to obstructive jaundice on liver damage. *Hepatogastroenterology.* 50(53): 1542-1546.

Salasidis R, Fleiszer T and Johnston R. (1998) Air insufflation technique of enteral tube insertion: a randomized, controlled trial. *Crit Care Med.* 26: 1036-1039.

Salman FT, Buyruk MN, Gürler N, *et al*. (1992) The effect of surgical trauma on the bacterial translocation from the gut. *J Pediatr Surg.* 27(7): 802-804.

Sanders ME. (2000) Considerations for use of probiotic bacteria to modulate human health. *J Nutr*. 130(suppl): 384S–390S.

Schatten WE, Desprez JD and Holden WD. (1955) A bacteriological study of portal vein blood in man. *Arch Surg.* 71: 404-409.

Schebendach J, Golden NH, Jacobson MS, *et al*. (1995) Indirect calorimetry in the nutritional management of eating disorders. *Int J Eating Disorders.* 17: 59–66.

Schleiffer R and Raul F. (1996) Prophylactic administration of L-arginine improves the intestinal barrier function after mesenteric ischemia. *Gut.* 39:194–198.

Schmidt W, Hacker A, Gebhard MM, *et al*. (1998) Dopexamine attenuates endotoxin-induced microcirculatory changes in rat mesentery: role of ß2 adrenoceptors. *Crit Care Med*. 26(10): 1639-1645.

Schoeffel U, Pelz K, Haring RU, *et al.* (2000) Inflammatory consequences of the translocation of bacteria and endotoxin to mesenteric lymph nodes. *Am J Surg.* 180(1): 65-72.

Schofield WN. (1985) Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr. Clin Nutr.* 39(Suppl. 1): 5–41.

Schweinberg FB, Seligman AM, and Fine J. (1950). Transmural migration of intestinal bacteria. A study on the use of radioactive *Escherichia coli*. *N Engl J Med.* 242: 747-751.

Sedman PC, MacFie J, Sagar P, *et al*. (1994) The prevalence of gut translocation in humans. *Gastroenterology.* 107(3): 643-649.

Seguin P, Le Bouquin V, Aguillon D, *et al*. (2005) Testing nasogastric tube placement: evaluation of three different methods in intensive care unit. *Ann Fr Anesth Reanim*. 24(6): 594-599.

Seidner DL and Ramasamy D. (2005) Enteral nutrition in intestinal failure. In: *Intestinal failure and rehabilitation: a clinical guide.* Matarese LE, Steiger E and Seidner DL (Eds.) pp. 209-227. CRC Press, New York.

Sellden E. (2002) Peri-operative amino acid administration and the metabolic response to surgery. *Proc Nutr Soc*. 61(3): 337-343.

Senkal M, Kemen M, Homann HH, *et al*. (1995) Modulation of postoperative immune response by enteral nutrition with a diet enriched with arginine, RNA, and omega-3 fatty acids in patients with upper gastrointestinal cancer. *Eur J Surg.* 161: 115–122.

Shipps FC, Sayler CB, Egan JF, *et al.* (1979) Fluoroscopic placement of intestinal tubes. *Radiology*. 132: 226-227.

Shou J, Lappin J, Minnard EA, *et al.* (1994) Total parenteral nutrition, bacterial translocation, and host immune function. *Am J Surg.* 167(1): 145-150.

Simon GL and Gorbach SL. (1986) The human intestinal microflora. *Dig Dis Sci.* 31: 147S-162S.

Slagt C, Innes R, Bihari D, *et al.* (2004) A novel method for insertion of post-pyloric feeding tubes at the bedside without endoscopic or fluoroscopic assistance: a prospective study. *Intensive Care Med.* 30(1): 103-107.

Smithies M, Yee TH, Jackson L, *et al.* (1994) Protecting the gut and the liver in the critically ill: effects of dopexamine. *Crit Care Med.* 22: 789-795.

Song F and Whitacre CC. (2001) The role of the gut lymphoid tissue in induction of oral tolerance. *Curr Opin Investig Drugs.* 2(10): 1382-1386.

Spahn TW and Kucharzik T. (2004) Modulating the intestinal immune system: the role of lymphotoxin and GALT organs. *Gut.* 53(3): 456-465.

Spindler-Vesel A, Bengmark S, Vovk I, *et al.* (2007) Synbiotics, prebiotics, glutamine, or peptide in early enteral nutrition: a randomized study in trauma patients. *JPEN J Parenter Enteral Nutr.* 31(2): 119-126.

Stroud M, Duncan H and Nightingale J. (2003) Guidelines for enteral feeding in adult hospital patients. *Gut*. 52 Suppl 7: vii1-vii12.

Tabachnick BG and Fidell LS. (1996) *Using multivariate statistics* (3rd edition). pp. 132. Harper Collins, New York.

Takesue Y, Ohge H, Uemura K, *et al.* (2002) Bacterial translocation in patients with Crohn's disease undergoing surgery. *Dis Colon Rectum.* 45(12): 1665-1671.

Takesue Y, Kakehashi M, Ohge H, *et al.* (2005) Bacterial translocation: not a clinically relevant phenomenon in colorectal cancer. *World J Surg.* 29(2): 198-202.

Tappenden KA. (2006) Mechanisms of enteral nutrient-enhanced intestinal adaptation. *Gastroenterology*. 130(2 Suppl 1): S93-99.

Taylor BN (ed). (1995) Guide for the Use of the International System of Units. *National Institute for Standards and Technology (NIST) Special Publication 811.* pp. 1-74. U.S. Government Printing Office.

Taylor BN (ed). (2001) The International System of Units (SI). *National Institute for Standards and Technology (NIST) Special Publication 330*. pp. 1-68. U.S. Government Printing Office.

Teitelbaum J and Walker WA. (2001) Review: the role of omega 3 fatty acids in intestinal inflammation. *J Nutr Biochem.* 12: 21–32.

Temmesfeld-Wollbruck B, Szalay A, Mayer K, *et al.* (1998) Abnormalities of gastric mucosal oxygenation in septic shock: partial responsiveness to dopexamine. *Am J Respir Crit Care Med*. 157: 1586-1592.

Thurlow P. (1986) Bedside enteral feeding tube placement into duodenum and jejunum. *JPEN J Parenter Enteral Nutr.* 10: 104-105.

Thurnham DI, Northrop-Clewes CA, McCullough FS, *et al.* (2000) Innate immunity, gut integrity, and vitamin A in Gambian and Indian infants. *J Infect Dis.* 182(suppl): S23–28.

Tighe D, Moss R, Heywood G, *et al.* (1995) Goal-directed therapy with dopexamine, dobutamine, and volume expansion: effects of systemic oxygen transport on hepatic ultrastructure in porcine sepsis. *Crit Care Med*. 23(12): 1997-2007.

Todorovic V, Russell C, Stratton R, Ward J, Elia M. (Eds.). (2003) In: *The 'MUST' explanatory booklet: a guide to the malnutrition universal screening tool ('MUST') for adults*. British Association of Parenteral and Enteral Nutrition (BAPEN).

Todorovic V and Micklewright A (Eds.). (2004) In: *A Pocket Guide to Clinical Nutrition.* pp. 3.1 - 3.20. British Dietetic Society.

Trager K, Radermacher P, Brinkmann A, *et al.* (2001) Gastrointestinal tract resuscitation in critically ill patients. *Curr Opin Clin Nutr Metab Care*. 4(2): 131-135.

Traut U, Brügger L, Kunz R, *et al.* (2008) Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults. *Cochrane Database Syst Rev.* 2008 (1): CD004930.

Travis SP and Menzies I. (1992) Intestinal permeability: functional assessment and significance. *Clinical Science.* 82: 471-488.

Tremel H, Kienle B, Weilemann L, *et al.* (1994) Glutamine dipeptide-supplemented parenteral nutrition maintains intestinal function in the critically ill. *Gastroenterology.* 107: 1595–1601.

Van der Hulst R, van Kreel B, von Meyenfeldt M, *et al.* (1993) Glutamine and the preservation of gut integrity. *Lancet.* 334: 1363–1365.

Vermeulen MA, van de Poll MC, Ligthart-Melis GC, *et al.* (2007) Specific amino acids in the critically ill patient--exogenous glutamine/arginine: a common denominator? *Crit Care Med*. 35(9 Suppl): S568-576.

Wakeling HG, McFall MR, Jenkins CS, *et al*. (2005) Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. *Br J Anaesth.* 95(5): 634-642.

Wapnir RA. (2000) Zinc deficiency, malnutrition and the gastrointestinal tract. *J Nutr.* 130(suppl): 1388S–1392S.

Wasiak J, Cleland H and Jeffery R. (2006) Early *versus* delayed enteral nutrition support for burn injuries. *Cochrane Database Syst Rev*. 2006 Jul 19;3: CD005489.

Watters JM, Kirkpatrick SM, Norris SB, *et al*. (1997) Immediate postoperative enteral feeding results in impaired respiratory mechanics and decreased mobility. *Ann Surg*. 226(3): 369–377 (discussion 377–80).

Weimann A, Bastian L, Bischoff WE, *et al*. (1998) Influence of arginine, omega-3 fatty acids and nucleotide-supplemented enteral support on systemic inflammatory response syndrome and multiple organ failure in patients after severe trauma. *Nutrition.* 14:165–172.

Welch SK, Hanlon MD, Waits M, *et al*. (1994) Comparison of four bedside indicators used to predict duodenal feeding tube placement with radiography. *JPEN J Parenter Enteral Nutr.* 18(6): 525-530.

Wells CL. (1990) Relationship between intestinal microecology and the translocation of intestinal bacteria. *Antonie Van Leeuwenhoek.* 58(2): 87-93.

Wells CL, van de Westerlo EMA, Jechorek RP *et al*. (1995) Exposure of the lateral enterocyte membrane by dissociation of calcium-dependent junctional complex augments endocytosis of enteric bacteria. *Shock.* 4: 204-210.

Wells CL, Erlandsen SL. (1996) Bacterial Translocation: Intestinal Epithelial Permeability. In: *Update in Intensive Care and Emergency Medicine (26): Gut Disfunction in Critical Illness*. (Rombeau JL, Takala J, eds.) pp. 137-145. Springer-Verlag.

Wen L, Tang W, Jiang Z, *et al*. (2000) Detection of bacterial DNA in blood with three pairs of primers. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao.* 22(6): 592-594.

Weissman C. (1990) The metabolic response to stress: an overview and update. *Anesthesiology.* 73: 308–327.

Wilmore DW. (2002) From Cuthbertson to fast-track surgery: 70 years of progress in reducing stress in surgical patients. *Ann Surg.* 236: 643-648.

Wind J, Polle SW, Fung Kon Jin PH, *et al*. (2006) Systematic review of enhanced recovery programmes in colonic surgery. Br J Surg. 93(7): 800-809.

Windsor JA and Hill GL. (1988) Protein depletion and surgical risk. *Aust N Z J Surg.* 156: 341-345.

Wischmeyer PE. (2006) Glutamine: role in gut protection in critical illness. *Curr Opin Clin Nutr Metab Care*. 9(5): 607-612.

Wischmeyer PE. (2007) Glutamine: mode of action in critical illness. *Crit Care Med*. 35(9 Suppl): S541-4.

World Health Organization. (1985) Energy and protein requirements. Report of a joint FAO/WHO/UNU expert consultation. *WHO Technical Report Series No. 724.* World Health Organization, Geneva.

Woodcock NP, Zeigler D, Palmer MD, *et al*. (2001) Enteral *versus* parenteral nutrition: a pragmatic study. *Nutrition*. 17(1): 1-12.

Woodcock N and MacFie J. (2002) Optimal nutrition support (and the demise of the enteral *versus* parenteral controversy). *Nutrition*. 18(6): 523-524.

Woodcock N and MacFie J. (2004) Optimal nutritional support. *Proc Nutr Soc*. 63(3): 451-452.

Young RJ, Chapman MJ, Fraser R, *et al*. (2005) A novel technique for post-pyloric feeding tube placement in critically ill patients: a pilot study. *Anaesth Intensive Care*. 33(2): 229-234.

Zaloga GP. (2005) The myth of the gastric residual volume. *Crit Care Med*. 33(2): 449-450.

Zamora E, Lupón J, Urrutia A, *et al*. (2007) Does body mass index influence mortality in patients with heart failure? *Rev Esp Cardiol*. 60(11): 1127-1134.

Zapas JL, Karakozis S and Kirkpatrick JR. (1998) Prophylactic jejunostomy: a reappraisal. *Surgery*. 124(4): 715-719; discussion 719-20.

Zigmond AS and Snaith RP. (1983) The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 67: 361-370.

Zmora O, Mahajna A, Bar-Zakai B, *et al*. (2003) Colon and rectal surgery without mechanical bowel preparation: a randomized prospective trial. *Ann Surg*. 237: 363-367.