INVESTIGATION OF DIARRHOEA IN CRITICALLY ILL PATIENTS RECEIVING ENTERAL NUTRITION

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SUMMARY

The incidence and causes of diarrhoea among critically ill patients receiving enteral tube feeding were investigated.

Sixty acutely ill surgical or medical intensive care patients who had had a minimum of 48 hrs bowel rest were entered into the study. They were randomly assigned to receive one of two lactose free liquid formula diets - "Ensure", a commercially available feed containing 825 kCal/L and 34 g/L of protein with an osmolality of 441mOsm/l or "Casilan Oil", a home-made feed containing 840 kCal /L and 45g/L of protein with an osmolality of 383 mOsm/l. The feeds were administered by constant nasogastric infusion. Patients received 1000ml at a rate of 40ml per hour for the first day and up to 2000ml at 80 ml per hour for the remainder of the study period.

Investigations included documentation of medical history, medications administered and clinical details for each patient. Serum albumin was measured and the nutritional status of each patient was assessed using anthropometric measurements. Feeds were tested for bacterial contamination on the three days following the start of feeding and small intestinal bacterial overgrowth was assessed by the 1g-^{14}C Xylose breath test of Toskes and King.

Twelve of the sixty patients had to be withdrawn from the trial within 24 hours of the start of enteral feeding for medical reasons. The remaining forty eight patients completed at least three days on enteral feeding and thereby became eligible for analysis. In 10/48 patients (21%) diarrhoea was present before enteral feeding began. Four of these 10 patients continued to pass loose stools when enteral feeding was started while the remaining 6 settled. Diarrhoea developed in a further 10 patients (21%) after enteral feeding began. The overall incidence of diarrhoea in the group of critically ill patients studied was therefore 42% (20/48). However, of the fourteen patients who experienced diarrhoea during enteral feeding four had diarrhoea before feeding began. Therefore, the true incidence of diarrhoea related to enteral feeding was only 10/38 (26%). Furthermore, in 7 of these 10 patients, another possible cause of diarrhoea was present.

There was no significant association between diarrhoea and nutritional status, hypoalbuminaemia, sepsis, length of bowel rest, sucralfate and antibiotic therapy other than amikacin.

Twenty one patients received Ensure and 27 received Casilan Oil. Despite the differences in the composition of the feeds, the incidence of diarrhoea was similar on the Ensure and the Casilan Oil. No particular factor pertaining to the composition of the feeds was associated with diarrhoea. Significant contamination of feeds was universal but there was no constant relationship between bacterial counts, or types, and the occurrence of diarrhoea.

Certain other factors were found to be significantly associated with diarrhoea. Abdominal injury was positively associated with the occurrence of diarrhoea ($p<0.05$). Diarrhoea could have been attributed to the underlying disease state in 7 of the patients.

All three patients who were receiving lactulose as treatment for liver failure developed diarrhoea. While no association was noted between diarrhoea and antibiotic therapy in general, treatment with the antibiotic, amikacin, correlated significantly, albeit marginally, with the occurrence of diarrhoea ($p<0.05$).

Twenty six patients were tested for small intestinal bacterial overgrowth. Only one patient, with an elevated excretion of $^{14}CO_2$, indicative of small intestinal bacterial overgrowth, developed diarrhoea. There was, however, a positive association between diarrhoea and decreased excretion of $^{14}CO_2$. It would appear that the bacterial flora was suppressed in patients with diarrhoea. Amikacin therapy was also associated with decreased excretion of $^{14}CO_2$. This may suggest that amikacin could have altered the bowel flora with resultant development of diarrhoea.

While abdominal injury and disease were associated with the development of diarrhoea and amikacin was a possible factor associated with diarrhoea, the results of the present study indicate that enteral tube feeding with either the commercial feed, Ensure or the home-made feed, Casilan Oil was not a cause of diarrhoea in the majority of critically ill patients assessed. Furthermore, in

most patients who commenced the trial with diarrhoea, improvement was noted on enteral feeding.

ABBREVIATIONS

cfu/ml	colony forming units per millilitre
ml	millilitres
g/l	grams per litre
mOsm/l	milliosmols per litre
cm	centimetre
mm	millimetre
^{14}C	^{14}C labelled carbon
$^{14}CO_2$	^{14}C labelled carbon dioxide
μCi	microcurie
mmol	millimole
l	litre
dpm	disintegrations per minute
S.D	standard deviation
p	probability
mg	milligrams
kg	kilograms
kCal	kilocalories
CHO	carbohydrates
PEM	protein energy malnutrition
MUAC	mid upper arm circumference
MUMC	mid upper muscle circumference
TPN	total parenteral nutrition
I.C.U	intensive care unit
C.O.A.D	chronic obstructive airways disease
P.T.B	pulmonary tuberculosis
A.R.D.S	adult respiratory distress syndrome
MVA	motor vehicle accident
Ca	cancer

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1. NUTRITIONAL SUPPORT IN THE CRITICALLY ILL

1.1. IMPORTANCE OF ADEQUATE NUTRITIONAL SUPPORT

The management of critically ill patients has been greatly improved during the last few decades. One of the most recent advances has been the recognition of the importance of adequate nutritional support for this type of patient[1]. This has been due to increasing awareness of the significance of protein and energy malnutrition in the acutely ill patient[1] as the presence of malnutrition associated with critical illness is known to increase the risk of morbidity and mortality[2].

Protein energy malnutrition has been shown to be common among hospitalized patients and in some surveys is reported to be as high as 50%[3,4,5,6]. A recent study done at Groote Schuur Hospital reported that 30 - 40% of hospitalized patients were malnourished[7]. Some patients enter the hospital in a state of malnutrition but others become malnourished during hospitalization. This occurs predominantly as a consequence of catabolic stress, surgery and sepsis but most disturbing of all, may be due to virtual starvation when patients are given only saline or dextrose solutions for prolonged periods[2].

Surgical injury, trauma or critical illness results in an increase in metabolic activity[1]. Stores of lean body mass can be lost due to protein breakdown and alterations in amino acid and carbohydrate metabolism[8] as glucose and protein have to be used as energy sources. Gluconeogenesis is fuelled by endogenous protein breakdown and oxidation. These stores can withstand a short period of severe stress but in the case of the malnourished or nutritionally depleted patient, serious losses of lean body mass may occur[1]. Loss of protein, particularly in the musculature involved with respiration, compromises pulmonary function and can result in inefficient ventilation[9]. Efficient wound healing and immunocompetence are also dependant on the availability of basic

nutrients[9], especially in the critically ill patient who is susceptible to infection. When associated with critical illness, progressive depletion of body reserves increases the possibility of death by sepsis or organ failure[10].

The aim of nutritional support during critical illness is primarily to minimise excessive loss of body stores and amino acids so that host mechanisms can be preserved. The provision of continuous nutritional support is vital to the recovery of the patient and when withheld could increase the possibility of prolonged sepsis, organ failure and death.

The question is not whether critically ill patients require nutritional support but how their nutritional requirements can be optimally met.

1.2. CHOICE OF NUTRITIONAL SUPPORT SYSTEM

Due to the nature of their disease or injury, the majority of critically ill patients are unable to ingest food normally for most of the time spent in intensive care. The alternatives are to provide either enteral feeding or intravenous parenteral nutrition.

a) Parenteral feeding

Total parenteral nutrition (TPN) is defined as the administration of nutrients other than via the gastrointestinal tract and is usually given to patients when the gut is unable to digest and absorb nutrients normally. Parenteral feeding can also be used to supplement other forms of nutritional support, especially in severely malnourished individuals. The major breakthrough concerning parenteral feeding occurred in 1967 and 1968 when Dudrick and Wilmore showed that total parenteral nutrition was feasible and effective in dogs, children and adults using a central venous line[11,12].

Complications

Many complications associated with TPN are potentially life threatening. Mechanical complications usually occur during subclavian vein catheterization. The most common of these is pneumothorax. Air embolism is a potentially fatal complication which may also occur during catheter insertion[13]. Catheter sepsis is probably the most common complication which occurs during parenteral feeding[14]. Metabolic complications such as hypo and hyperglycaemia as well as electrolyte abnormalities may also occur.

Parenteral nutrition , either on its own or in conjunction with other forms of nutritional support is now widely used to support patients who require specialized nutrition. However, due to the high cost of parenteral nutrition as well as the associated complications, it has been recommended that the gut should be used whenever possible[15].

b) Enteral feeding

Enteral feeding is defined as the provision of liquid diets by tube or mouth into the gastrointestinal tract[16].

The practice of providing nutrition by way of an inserted tube is first thought to have been used in early Egyptian times when monthly nutrient enemas were considered to be essential for health. The first documented case of a patient fed directly into the oesophagus by way of a tube dates back to 1598 when Cappiveccius is reported to have administered nutrients via a tube attached to an animal bladder[15].

The food or "nutritious liquids" which were given to the patients consisted mainly of milk, eggs, broth, meat extracts and invariably a little wine or brandy. The feeds were administered in large bolus amounts using what we would consider to be a rather barbaric method. The patient was held down and his nostrils pinched until he gasped for air. At this point the tube was inserted into the mouth and the "nutritious liquids" expressed into the oesophagus. The reason for the addition of alcohol now becomes clear!

Fortunately this method of providing nutrition was greatly modified and improved and by 1874 softer, more flexible tubes were used and the procedure had therefore become slightly less traumatic. Also, naso-oesophageal feeding rather than feeding by mouth became more popular during the latter part of the 19th century. Enteral feeding was widely used to feed patients who refused to eat, particularly those in asylums for the insane. In his article on the history of enteral feeding, Randall mentions that the deliberate feeding of large quantities of liquidised food in order to produce weight gain became more popular in the late 19th century when Dr Dubove reported weight gain and significant clinical improvement in a group of malnourished patients with tuberculosis. Morison also reported improvement in a group of 28 children with diphtheric paralysis of the throat, who were given forced enteral feeding[15].

By the end of the 19th century, tube feeding into the stomach was well established. In addition it had been suggested that feeding smaller amounts more often decreased the feelings of bloating and epigastric distress experienced by patients[15].

Since the beginning of the 20th century tube feeding has been used as a regular procedure in specific diseases[17]. Randall remarks that the importance of enteral feeding for ill patients, particularly the malnourished, was first documented by Parera in 1959 when he emphasised the relationship between anorexia and starvation and stressed the importance of nutritional support[15].

During the last three decades in particular, major advances and improvements have been made to both the method of providing enteral tube feeding and to the feeds used. Enteral feeding now forms an integral part of the overall treatment of ill patients. It is no longer used only for patients who refuse to eat or who need to gain weight, but in addition, is used in any situation where the gut is functional but the patient is unable to take food normally.

Types of enteral feeds

A wide variety of enteral feeds is now commercially available. In addition to the traditional milk based feeds, a number of specialised products exist which are designed to meet the specific needs of particular disease groups. These range from basic polymeric diets containing whole protein, carbohydrate and fat from

sources such as casein, corn starch and oil, to the so-called elemental diets which consist of predigested nutrients in the form of glucose complexes, crystalline amino acids, protein hydrolysates and fatty acids[18]. Lactose free feeds have also become popular due to the incidence of adult lactose intolerance. Most of the commercial feeds are in powder form and have to be reconstituted using either milk or water. There are a few sterile liquid feeds available but these are usually more expensive. Due to the higher cost of commercial feeds, home-made feeds consisting of milk, eggs and sugar or a variety of specialised ingredients which can be bought commercially, remain popular in many institutions. Normal, liquidised food can also be used[17]. There is , however, evidence to suggest that home-made feeds are associated with unacceptable contamination[19] and an increased occurrence of diarrhoea[20].

At Groote Schuur Hospital the commercially available product, Ensure, is the most commonly used enteral feed. It is in powder form and has to be reconstituted using water. Another feed, Casilan Oil, which is home made, is also popular, and in contrast to the findings of Keighley et al[20] regarding home-made feeds, has anecdotally been found to be effective in curtailing diarrhoea in patients who cannot tolerate Ensure. This has, however, not been clinically proven.

Feeding techniques

The time honoured method of bolus feeding up to 200 ml of feed at one time, via large bore nasogastric tubes remains the most common method of administration of enteral feeds[21]. Since 1976, a number of clinicians have recommended the use of continuous feeding rather than bolus[18,22,23]. This has been mainly due to the development of fine bore feeding tubes and specialised feeding pumps. In addition, concern has been expressed about the rate at which bolus feeds are administered as gastrointestinal complications are more likely to occur when large volumes of feed are administered too quickly[24,25]. Hiebert et al compared bolus feeding to continuous and found that patients on continuous feeding had significantly decreased stool frequency compared to those on bolus feeding[26]. Although there is little evidence to suggest that one technique is physiologically superior to the other, studies have shown that continuous feeding is superior in terms of nutrient delivery and avoidance of side effects[18,27]. When continuous feeding is used rather than bolus, the rate

of infusion of the feed may be controlled using either specialised infusion pumps or the constant gravity drip method where the rate is controlled with the use of a roller clamp.

The first tubes used to provide nutrition enterally consisted of substances such as eel skin, silver and indian rubber[28]. Until the 1950's feeding tubes were stiff and large and extremely uncomfortable for patients. With the introduction of poly-ethylene and poly-vinyl in the 1950's and 1960's, softer, more flexible tubes were developed. Silicone elastomer tubes were first used towards the end of the 1960's. During the 1970's polyvinyl was replaced by poly-urethane and today the majority of enteral feeding tubes are made from either poly-urethane or silicone elastomer. As the tubes are extremely soft and pliable, a guide wire is usually necessary for passing such a tube into the stomach. Tubes may vary in width from 6 to 18 French. The most popular size for fine bore nasogastric feeding is the 8 French but often large bore Ryle's tubes which are 12 to 16 French are used instead. Although there are no controlled studies which have compared large bore to fine bore tubes, the large bore tubes are associated with more complications than the fine bore type of tubes[29]. Complications associated with large bore tubes include gastric erosion, acute sinusitis, oesophagitis and nasopharyngeal discomfort to mention a few. Fine bore tubes may be easily displaced or misplaced and blockage of viscous feeds may occur. Aspiration of feeds is also more common when fine bore tubes are used.

Feeding via a nasogastric tube remains the most popular route of feeding, but feeds are also infused into the jejunum with the use of special long tubes. Direct feeding into the stomach or jejunum via gastrostomy or jejunostomy is another alternative[30].

In the intensive care units at Groote Schuur Hospital, the enteral feeds are infused primarily using the continuous method and the nasogastric route. Wide bore (16 French) Ryle's tubes are used in preference to the fine bore tubes due to the possible complication of aspiration of feed into the lungs. In addition, oral medication often has to be given via the tube and wider tubes are therefore preferred.

Complications

There are relatively few significant complications associated with enteral feeding. Potentially the most serious is aspiration of feed into the lungs[31,32]. Diarrhoea is the most common side effect associated with enteral feeding and tube feeding per se has gained a certain notoriety for its tendency to produce diarrhoea[33,34]. Gastrointestinal side effects such as nausea, vomiting and abdominal cramps are reported to occur in 10 - 15% of patients receiving enteral tube feeding but are more likely to occur on bolus feeding[34,35,36]. Constipation is known to occur in patients on long-term enteral nutritional support and this is probably due to the low fibre content of most enteral feeds[37]. Metabolic complications such as hyperglycaemia, dehydration and electrolyte abnormalities have been associated with enteral feeding but these are often due to inappropriate choice and careless preparation and administration of the feed[38,39]. Although enteral tube feeding is associated with some side effects, these are not potentially as serious as the complications which may occur during intravenous nutritional support.

c) Enteral or parenteral?

Ideally, the provision of adequate nutrition to the hospitalized patient should be the responsibility of a team consisting of doctors, dietitians and nurses who should make the decisions concerning the type of nutrition and method of administration to be used in any particular case[40]. Patients should be continually monitored for signs of intolerance as well as to ascertain the efficacy of the nutrition being provided.

It is widely acknowledged that if there is any function in the gastrointestinal tract, it should be used[1,16]. Animal trials have shown that enteral feeding is as effective as intravenous in maintaining or improving nutritional status[41,42,43]. Further animal studies have demonstrated that the intraluminal delivery of nutrients is necessary for the maintenance of gastrointestinal integrity[44,45]. Although only a few studies have been done in humans comparing enteral to intravenous feeding, the majority of those done confirm that the nutritional requirements of patients with some functioning gut can be met by suitable enteral feeding[46,47]. The cost of enteral nutrition is also considerably lower

than that of parenteral nutrition. One day of intravenous feeding costs a minimum of R80 compared to R8 per day on enteral feeding.

Enteral feeding is a safe, cheap method of providing effective nutritional support. The major complication associated with enteral feeding is diarrhoea. In this study, the effects of enteral feeding, particularly with respect to diarrhoea, have been investigated.

2. DIARRHOEA IN CRITICALLY ILL PATIENTS

2.1. INTRODUCTION

Diarrhoea has been defined as an increase in stool frequency and/or volume or a decrease in stool consistency[29]. It is frequently associated with excessive faecal water loss caused by either reduced absorption or increased secretion of water.

Diarrhoea is predominantly the result of decreased absorptive capacity of the gastrointestinal tract, increased secretion of solute or a combination of abnormalities of absorption and secretion.

When a poorly absorbable substance is ingested, the result is that water is drawn into the intestinal lumen. This retention of water could cause an osmotic type of diarrhoea. Substances which may cause such diarrhoea include osmotic cathartics, magnesium salts such as those used in antacid preparations, and lactulose. Carbohydrate malabsorption such as that which occurs in lactose intolerant individuals, as well as after extensive intestinal resection, may also cause osmotic diarrhoea.

Secretory diarrhoea occurs when endogenous secretion of solutes such as bile acids and fatty acids is increased. This may occur after resection of the distal ileum or cholecystectomy. Both bacterial endotoxins and laxitives may cause alterations in ion transport and increased secretion of electrolytes. This in turn results in passive diffusion of water into the lumen and may cause diarrhoea[48].

The absorptive capacity of the gastrointestinal tract is decreased when structural damage to the mucosa occurs. Ischaemia and inflammatory bowel disease, including Crohn's disease and ulcerative colitis could cause such damage.

Acute diarrhoea is one of the most common afflictions known to man. It is, however, often difficult to establish the aetiology due to the many possible causes of such diarrhoea.

2.2. INCIDENCE

Although there are few published articles concerning the incidence of diarrhoea among critically ill patients, the impression has arisen that the incidence is high. In 1976 Woolfsen et al[35] reported that approximately half of a group of 15 critically ill patients developed diarrhoea. A study done by Kelly et al[31] demonstrated that 41% of intensive care patients developed diarrhoea for one or more reasons and Brinson and Kolts[49] showed a 34% incidence in a group of critically ill patients. In a recent study done by Hart and Dobb[50], 56% of critically ill patients developed diarrhoea. Griebe et al[51] however reported that only 20 of 112 (17%) patients in intensive care had diarrhoea. The emphasis has now been placed on establishing whether a primary cause of this diarrhoea exists, and if so, whether it can be identified.

2.3. FACTORS WHICH COULD INDUCE DIARRHOEA

a) Disease

Primary diseases associated with diarrhoea in adults include diseases of the gastrointestinal tract such as inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, ulcerative colitis, Zollinger Ellison syndrome, acute infectious enteritis, intra abdominal abcesses, chronic or acute pancreatitis and carcinoma or lymphoma of the bowel[51]. The mechanisms whereby diarrhoea occurs in these syndromes have been discussed previously.

Diarrhoea may also occur in syndromes such as lactose intolerance, tropical or non-tropical sprue, viral gastroenteritis, bacterial overgrowth and ischaemia[48]. Both chronic and intermittent diarrhoea may occur in patients with juvenile onset diabetes[52] and patients with renal failure may suffer from acute watery diarrhoea[48].

Iatrogenic causes of diarrhoea include abdominal surgery such as gastrectomy[53], ileal resection[54] and jejunal bypass[55] as well as radiation therapy to the bowel and drug therapy.

b) Drug therapy

Drugs commonly associated with diarrhoea include antibiotics, magnesium containing antacids, lactulose, corticosteroids, antihypertensive drugs such as guanethidine, diuretics, digitalis, quinidine, salicylazosulfapyridine, colchicine, biguanides, cholinergic drugs, gold compounds and opiates[48]. Laxatives are obviously associated with diarrhoea.

Antibiotics and anti-ulcer agents are the most frequently used of the above in the treatment of critically ill patients.

Antibiotics

Mild diarrhoea is a common adverse reaction associated with antibiotic therapy[48]. Treatment with antibiotics can result in qualitative and quantitative alteration of the normal bowel flora[56]. This may lead to malabsorption of nutrients particularly fat and vitamin B12 and may in turn cause diarrhoea. In addition oral antibiotics can directly affect the bowel mucosa and thus disturb normal gut function[56].

Pseudomembranous colitis is a potentially serious complication of antibiotic therapy. Most forms of antibiotic predispose the gut to the growth of Clostridium difficile, the organism which produces the toxin responsible for pseudomembranous colitis. Recently some cases of antibiotic-associated diarrhoea have been reported to be associated with the cytotoxin of Clostridium difficile[48,57,58]. Lincomycin and clindamycin in particular, were significantly associated with pseudomembranous colitis[57].

Tetracyclines have been shown to most frequently cause diarrhoea[56]. Similar findings are reported for lincomycin, clindamycin and ampicillin[31].

Oral antibiotic therapy is more likely than parenteral to affect both the bowel mucosa and the bowel flora[56]. Studies by Woolfsen et al[35] and Keohane et al[59] have demonstrated that there is a positive association between oral antibiotic therapy and diarrhoea. Kelly et al[31] however reported no causal relationship between intravenous antibiotic therapy and the incidence of diarrhoea.

A recent editorial in the British Medical Journal suggested that antibiotics be considered as a potential cause in all patients who develop diarrhoea[60].

Anti-ulcer therapy

Anti-ulcer agents such as H_2 receptor antagonists and antacids are often used to prevent stress ulceration in critically ill patients[31]. The latter comprise a variety of substances including sodium bicarbonate, calcium carbonate, aluminium hydroxide and magnesium. Side effects associated with the use of antacids include sodium overload, hypercalcaemia and phosphate depletion. In addition the magnesium containing preparations may lead to severe diarrhoea[61]. The relationship between anti-ulcer agents and diarrhoea with particular regard to bacterial overgrowth will be discussed in the following section.

Lactulose

Lactulose is an indigestible synthetic disaccharide which is commonly given to patients in severe liver failure. The lactulose is converted to lactic acid which affects the pH of the intestine. This change in pH affects the bacteria which produce ammonia. Diarrhoea is a well known side effect of lactulose treatment[48].

c) Small intestinal bacterial overgrowth

In healthy humans, the luminal contents of the upper small bowel have a sparse microflora population i.e. < 10^5 organisms/ml. These are primarily gram +ve staphylococci, streptococci, lactobacilli and fungi. Coliforms and anaerobic organisms rarely occur in the normal small intestine[62,63,64]. The mechanisms controlling the gut flora population are not clearly understood, but are thought to include gastric acid secretion, intestinal motility, mucus products of bacterial metabolism and immunoglobulins[62].

When bacterial overgrowth occurs there is a dramatic increase in the number of both aerobes and anaerobes present in the ileum and jejunum. Small intestinal bacterial overgrowth is most commonly seen in patients with surgically produced blind or recirculating loops. This is often referred to as the "blind loop syndrome"[66].

Although bacterial overgrowth is most commonly associated with surgically constructed blind loops, any factor which results in an alteration in anatomy or motility of the small bowel or which kills intraluminal bacteria has the potential to cause bacterial overgrowth[62]. There are factors such as long term ileus and the prolonged administration of various forms of medication which, in conjunction with bacterial overgrowth, might predispose critically ill patients to diarrhoea[31]. In particular, antibiotics, antacids and H_2 receptor antagonists may alter the normal bowel flora. Antibiotics selectively kill certain strains of bacteria and allow others to proliferate.

H_2 receptor antagonist or antacid treatment decreases acid production in the stomach, with a resultant increase in pH[68]. Alteration in pH may affect the quantity and quality of the gastrointestinal flora[69] and has been associated with overgrowth of bacteria in the small intestine[67]. Treatment with the H_2 receptor antagonist, cimetidine, in particular, has been associated with both small intestinal bacterial overgrowth[70] and with diarrhoea[31,67].

Bacterial overgrowth in the small intestine is known to affect fat absorption. In the presence of bacterial overgrowth, fat malabsorption occurs primarily due to altered bile salt metabolism[62].

The effect of bacterial overgrowth on carbohydrate absorption is not established. Toskes and King showed that diminished urinary xylose excretion after an oral xylose excretion test in the rat blind loop syndrome was due to the bacterial catabolism of xylose to carbon dioxide[71]. Similar studies in humans have revealed a significantly increased catabolism of ^{14}C-d-xylose to $^{14}CO_2$ in patients with bacterial overgrowth[72]. Indeed this forms the basis of one of the tests used for identifying small intestinal bacterial overgrowth. Intraluminal fermentation of carbohydrate is thought to occur, as increased levels of volatile short chain fatty acids have been measured in the presence of overgrowth[73]. Investigations with the blind loop rat model have shown a decreased in vitro uptake of monosaccharides and a decreased in vivo absorption[74,75].

Increased flux of protein across the mucosa into the lumen has been a consistent finding in both the rat model and occasionally in humans with the blind loop syndrome[77,78]. Increased urinary excretion of indicans and phenols has been used as a test for detecting the presence of bacterial overgrowth[76].

In summary, malabsorption of nutrients is known to occur in the small bowel in the presence of bacterial overgrowth and can result in diarrhoea.

d) Bowel rest, sepsis and shock

The majority of patients in intensive care have experienced severe shock due to either surgery, trauma or sepsis. The ileus associated with the above conditions results in a period of bowel rest. Periods of fasting are known to result in a decrease in both villous height and cell proliferation in animal models[13], and long term bowel rest is known to cause villous atrophy of the gastrointestinal tract in man[79,80]. Even when complete nutritional support is provided intravenously, structural and functional atrophy may occur[81,82,83] with decreased secretions of enzymes such as sucrase, maltase, lactase and galactokinase[81,84]. Commencement of feeding in this situation could therefore result in malabsorption and diarrhoea.

e) Infectious diarrhoea

Infection with intestinal pathogens such as salmonella, shigella, campylobacter and escherichia coli species can induce diarrhoea in critically ill patients. Consequently, stools should always be sent for culture[31,58].

f) Protein Energy Malnutrition

Protein energy malnutrition (PEM) and kwashiorkor in children, have been associated with atrophy of the intestinal villi[85,86]. In primates in whom PEM has been experimentally induced, structural changes of the small intestine have been reported[87]. Studies in man have also demonstrated an alteration in gut structure in the presence of PEM[88-91]. For example, Tandon et al reported blunting of the villi and inflammatory cell infiltration in the majority of a group of malnourished individuals. Following treatment with a high protein diet these mucosal abnormalities improved progressively[89]. Platt and co-workers have demonstrated that pigs fed diets markedly low in protein, developed mucosal atrophy and diarrhoea[92].

Pancreatic function is reduced in children with kwashiorkor and marasmus and can lead to maldigestion[93]. In addition, O'Keefe et al have shown reduced pancreatic enzyme secretion and synthesis in an adult patient with severe malnutrition[94].

Protein deficiency in adults can therefore lead to intestinal alterations such as flattening of the villi and decreased secretion of digestive enzymes[95,96]. Such changes in gut structure and function could clearly predispose to malabsorption and diarrhoea.

g) Vitamin A deficiency

Probably the most recent factor which has been implicated in the aetiology of diarrhoea in critically ill patients, is vitamin A deficiency. Lack of vitamin A has been shown to predispose burn patients to the development of diarrhoea[97,98]. Vitamin A deficiency can cause changes in the metabolism of epithelial tissues and can therefore cause thinning of the gut epithelium and loss of mucous secretion[99,100]. A relationship between vitamin A deficiency and diarrhoea has been previously suggested in children[101,102].

h) Hypoalbuminaemia

One of the more recent publications concerning causes of diarrhoea in critically ill patients was that by Brinson et al[49]. It was reported that hypoalbuminaemia i.e. a serum albumin concentration of less than 26g/L was invariably associated with the occurrence of diarrhoea. A previous study by Cobb et al demonstrated that serum albumin levels of less than 30 g/L significantly correlated with the development of diarrhoea at the start of feeding[103].

Hypoalbuminaemia is thought to have the potential to cause diarrhoea due to intravascular volume expansion, which is the result of a reduction in plasma oncotic pressure. This, in turn, is caused by malnutrition, protein loss or haemodilution by excessive fluid infusions[49]. Volume expansion on its own has caused diarrhoea in experimental animals[104]. Hypoalbuminaemia in ICU patients is common and results from shifts in fluid balance and fluid space losses rather than malnutrition.

i) Enteral feeding

Results of various studies attempting to establish an association between diarrhoea and enteral tube feeding, are varied and contradictory. Woolfsen et al[35], Peaston[34] and Broom and Jones[65] reported a low incidence of tube feed related diarrhoea among critically ill patients receiving specially designed home-made feeds. Kelly et al[31] and Brinson and Kolts[49] have, however, reported a strong positive association between enteral tube feeding and the occurrence of diarrhoea. In the latter studies, 67% of the patients who were receiving the commercially available enteral solutions developed diarrhoea. The most recent publication concerning diarrhoea and tube feeding is that by Gottschlich et al[97]. The authors suggest that incidence of diarrhoea on enteral feeding may vary depending on the amount of fat present in the enteral feeds.

There are a number of factors related to enteral feeding which could cause diarrhoea. Properties of the feed itself such as significant bacterial contamination[105,106], high lactose content[33,107], excessive amounts of fat[108,109] and high osmolality[110.111.112] have all been associated with diarrhoea. In addition conditions of administration such as feeds given at very low temperatures[65,114] or rapid infusion rates[115] have been shown to be possible causes of diarrhoea.

Bacterial contamination

Food carries certain strains of bacteria which are harmless but if food infected with pathogenic organisms is ingested, harmful side effects including diarrhoea may occur. The accepted level of contamination by bacteria of non-sterile food is 100 colony forming units/ml (cfu/ml) and it is recommended that food containing more that 200 cfu/ml should be rejected[116]. Similar criteria are applied to reconstituted enteral feeds. Certain bacteria such as Escherichia coli, Salmonella, Staphylococcus aureus, Clostridium spp and Klebsiella should not be present in reconstituted tube feeds[116]. Most of these organisms occur normally in the body, particularly in the nasal passages and the large intestine[117]. Contamination of feeds by these organisms is therefore often indicative of poor hygiene.

Contamination may occur at any stage of preparation or administration, and the composition of enteral feeds is such that micro-organisms grow luxuriantly if introduced into the fluid. Particular factors associated with contamination of enteral feeds are mixers and liquidisers, contaminated working surfaces and probably most important of all, contaminated staff[118]. Bastow et al[119] have shown that diets blended in the diet kitchen are more likely to become contaminated.

Many studies have demonstrated that bacterial contamination of enteral feeds is common[105,120-124]. Anderton[118] reported contamination of both hospital and commercial feeds to exceed 10^9cfu/ml. Casewell[123] reported that a large proportion of feeds given to patients in intensive care were contaminated with up to 8×10^6 cfu/ml. The most common organisms found in the various feeds investigated in these studies were Klebsiella, Enterobacter, Acinetobacter and Bacillus species. Sixty eight per cent of feeds were found to contain Klebsiella species in the study conducted by Casewell[123]. While not usually implicated in diarrhoea, Kelly remarks that Pottecher is of the opinion that Gram-negative bacteria cause diarrhoea in critically ill patients[31]. In the study by Anderson et al[105], an association was noted between the extent of contamination and the incidence of diarrhoea although contamination was not invariably associated with diarrhoea. In the same study, other possible causes of the diarrhoea were

not investigated and contamination cannot therefore be cited as the only possible cause.

Casewell et al[124] have reported a case of septicaemia resulting from bacterial contamination of a tube feed but in general, bacterial contamination has not been associated with serious clinical complications[106]. Concern has however been expressed over the possible role of nasogastric feeds as potential sources of cross infection, especially in patients in intensive care[123]. There has also been speculation that contaminated feeds with bacterial counts as low as 10^4 cfu/ml can cause colonisation of the digestive tract and that this could result in infection by organisms such as E.coli, Klebsiella and Pseudomonas species. Critically ill patients treated with antibiotics, steroids and immunosuppresive agents might be prone to this type of infection[106].

Contamination of enteral feeds remains a problem, especially as in the majority of state financed hospitals, non-sterile feeding systems are used due to the cost of the commercially available sterile systems. However, although contamination of enteral feeds has been associated with diarrhoea, there is no clear-cut evidence to suggest that this is a cause and effect relationship.

Lactose

A considerable proportion of healthy adults is intolerant of the carbohydrate, lactose, due to a deficiency of the enzyme, jejunal beta-galactosidase which is responsible for the digestion of lactose to glucose and galactose[125]. Lactose cannot be absorbed intact and when jejunal beta- galactosidase is not present, the unabsorbed lactose remains in the gut lumen. The presence of the lactose causes an increase in osmotic pressure and fluid is drawn into the lumen. This in turn results in increased transit rate of the bowel contents and, commonly, diarrhoea. Bacteria also ferment the lactose in the large intestine to lactic acid, fatty acid, hydrogen and methane and this further exacerbates the symptoms[126].

Asian, African and Jewish population groups are particularly prone to maldigestion of lactose[127]. O'Keefe et al have reported a very high incidence of lactose intolerance among black South Africans[125,128]. One study reported that 90% of a random group of South African Zulus had abnormal lactose tolerance

tests[128]. Walike and Walike reported that 60% of Black Americans are lactase deficient[129]. Lactose intolerance is relatively uncommon among Caucasians and occurs in approximately 6% of the European population[130]. Six to 20% of white Americans are reported to be intolerant of lactose[129]. The effect of acute illness and malnutrition on gastrointestinal absorption and digestion is largely unknown. Mucosal jejunal beta-galactosidase activity may be temporarily depressed and the result would be decreased lactose digestion[131,132]. Malnutrition, intestinal resection, radiation enteritis and infectious diarrhoea may reduce the lactase content of the bowel[92].

Initially, many tube feeds were milk-based and therefore contained significant quantities of lactose. It has been suggested by Hindmarsh and Clark[107] that lactose could have been a cause of the diarrhoea associated with a jejunostomy feed used by Masterton, Dudley and Macrae[134]. In addition O'Keefe et al have shown that lactose containing liquid formulae were poorly tolerated by malnourished black African patients whereas lactose free formulae were well tolerated[135]. Walike and Walike reported that 87% of patients given a large lactose load such as that typically found in milk-based formulae, developed diarrhoea[129]. Consequently, a number of lactose free enteral feeds are now commercially available.

Fat

The use of low fat diets for patients who are prone to developing diarrhoea has been reported[136,137]. Anderson et al[137] reported a significant decrease in diarrhoea in a group of patients with Crohn's disease when given a low fat diet. In another study, burned guinea pigs were fed on either a low fat diet (i.e. fat = 30% of nonprotein calories) or a high fat diet (i.e. fat = 50% of nonprotein calories). Significantly more in the group on the 50% diet, developed diarrhoea[136]. Gottschlich et al demonstrated that a low fat diet (13.5 g/l) was associated with a 16% probability of diarrhoea, compared to a 62% probability on a feed with a fat content of 33 g/l, in a group of burns patients[138]. The results of a recently published article by Gottschlich et al substantiate these findings as less gastrointestinal intolerance was noted on a low fat regime (13 g/l)[97]. It is difficult to ascertain from the data presented in the latter study what the effect was on the incidence of diarrhoea when the feeds containing

intermediate amounts of fat were used. It is also notable that the other feeds used in this study contained unusually high proportions of fat (i.e. 65 - 80 g/l).

Fat maldigestion is known to occur when pancreatic enzyme digestion is significantly reduced. This is commonly seen in patients with acute or chronic pancreatitis and can result in an osmotic type of diarrhoea[97]. In addition, gastric surgery may delay the release of lipase and prevent adequate mixing of the lipase with the bowel contents[29].

Where patients do not have pancreatic insufficiency, another mechanism whereby a high fat diet could cause diarrhoea has been suggested[97]. Prostaglandins are known to affect bowel motility[140,141] and intestinal ion and water secretion[142,143] and increased levels could therefore induce diarrhoea. The fatty acids esters of arachidonic and linoleic acids, found predominantly in vegetable oils, are precursors in the biosynthesis of prostaglandins. One can but speculate as to whether prostaglandin overproduction, following intake of large amounts of such oils, may be a factor in diarrhoea.

Osmolality

A hypertonic solution delivered directly into the small bowel may cause passive diffusion of water into the intestinal mucosa and therefore cause diarrhoea[29]. High osmolality has been implicated as a cause of diarrhoea in enterally fed patients[133,134]. The introduction of full strength hypertonic formulae at the start of feeding in particular, was considered to be the major reason for the diarrhoea[144,145,146]. Consequently, "starter regimens" were introduced. For the first 3 - 5 days of feeding patients were given feeds which had been diluted to quarter or half strength. The osmolality was then gradually increased until full strength was tolerated.

The value of "starter regimens" in avoiding gastrointestinal side effects remains a controversial issue. Recent studies have shown that such regimens are unnecessary and result in poor nutritional intake. Feeds should, however, be given as a constant infusion rather than in bolus amounts. Keohane et al reported that administration of a hypertonic, polymeric enteral feed (<430 mOsm/l) to patients with normal gastrointestinal function, was not associated with diarrhoea[59]. Rees et al reported similar results using an elemental diet (630 mOsm/l) given to patients with impaired gastrointestinal function[147]. Zarling et al showed that enteral feeds with osmolalities varying between 325 and 690 mOsm/l were well tolerated by healthy individuals[148]. Ruppin et al examined potential side effects of hypertonicity of enteral diets and concluded that osmolality was not a cause of gastrointestinal side effects[149].

It has therefore been recommended that the use of starter regimens be abandoned when elemental as well as polymeric diets are used, provided administration is continuous rather than intermittent[59,110,111].

Case et al have demonstrated that rapid equilibration of dietary osmolality occurs in the stomach and duodenum in healthy individuals and it is suggested that differences in absorption rates of diets with different osmolalities are a function of the carbohydrate source in the diet rather than the direct effect of the osmolality[112].

Temperature of the feed

It has been recommended that feeds should be given at room temperature as the bolus administration of a cold feed can produce abdominal cramps and diarrhoea[65,110,114]. Prewarming of feeds is, however, not recommended due to the increased risk of bacterial contamination[118]. If continuous drip feeding is used, the refrigerated feed should attain room temperature within a short time.

Administration of the feed

Before the introduction of fine bore feeding tubes, bolus feeding of 200 - 600 ml, 4 - 8 times a day, was the accepted method. Recent surveys done in the U.S.A continue to indicate that many patients receiving enteral nutrition still receive bolus type feeding usually given in less than 20 minutes per feed[115]. Bolus feeding can cause rapid and uncontrolled emptying into the small bowel and can therefore induce diarrhoea[33,36,144]. The use of fine bore feeding tubes and infusion pumps makes it possible to feed patients at a continuous rate. The result is that the change in osmotic load is not as great, and the likelihood of diarrhoea occurring is reduced. Studies by Woolfsen et al[35], Dobbie and Butterick[150], McHugh and Moran[36] and Hiebert et al[26] have provided clear evidence in favour of the continuous feeding method compared to the bolus method. In a study by Heitkemper et al[115], normal volunteers experienced more abdominal discomfort and nausea when feeds were administered at fast infusion rates and the larger feeding volumes significantly affected the time taken for gut motility to return to normal. Although Jones et al[151] reported that more than 85% of patients were fed successfully by simple gravity infusion, feeding pumps facilitate the maintenance of a constant rate of infusion.

Carefully controlled conditions of administration of feeds should minimise the risks of side effects associated with enteral feeding.

CHAPTER 2

RATIONALE FOR AND OBJECTIVES OF THIS STUDY

RATIONALE

Adequate nutrition is of vital importance in the care of critically ill patients. Diarrhoea in such patients can result in malabsorption of vital nutrients and fluid, and exacerbate an already critical situation.

As mentioned before, there are few published articles concerning diarrhoea in critically ill patients. The results of these studies are varied and contrasting, especially in relation to the possible association between enteral feeding and diarrhoea. In particular, controversy exists relating to the differences between home-made and commercial feeds and their effect on diarrhoea.

It should be noted that the studies mentioned above have been done over a period of twenty years. During this time there have been numerous advances made with regard to enteral feeding techniques and types of feeds as well as to the overall treatment of critically ill patients. Therefore, in view of the large number of variable factors associated with these studies, it is not possible to draw any clear-cut conclusion from the available literature as to whether the diarrhoea is due to the "tube feeding" itself, whether choice of feed and method of administration are important factors or whether there are other more important causes which are unrelated to enteral feeding.

The prevalence and common causes of diarrhoea among critically patients have not been previously investigated at Groote Schuur Hospital. However, clinical experience has led medical and nursing staff at this hospital to believe that the prevalence is high, especially among patients receiving enteral nutrition. Enteral feeding has aquired a reputation for being the most probable cause of the diarrhoea. Consequently, enteral nutritional support is either substantially reduced or temporarily stopped when diarrhoea occurs. Sometimes total parenteral nutrition is introduced instead but frequently patients do not receive optimum nutritional support for a number of days. In addition, initiation of

enteral feeding is often delayed when patients already have diarrhoea as the feeding is assumed to exacerbate the situation. It is a cause for concern that enteral nutritional support is delayed, withdrawn or reduced in the event of diarrhoea occurring when it has not been unequivocally established that the enteral feeding is the only possible cause of the diarrhoea.

OBJECTIVES

On the basis of this rationale it was decided to:

(1) investigate the prevalence of diarrhoea in critically ill patients

(2) examine the possible association between the prevalence of diarrhoea and enteral feeding

(3) establish whether choice of enteral feed affected the prevalence of diarrhoea by comparing a home-made feed (Casilan Oil) to a commercial feed (Ensure)

(3) examine whether there was an association between any of the other factors outlined above and the incidence of diarrhoea.

CHAPTER 3

PATIENTS AND METHODS

1. PATIENT SELECTION AND MONITORING

All patients commencing tube feeding in both the surgical and the respiratory intensive care units were considered for inclusion in the trial. Patients who had diarrhoea at the time the feeding was commenced were not excluded as it was important to ascertain whether enteral feeding affected the severity of diarrhoea. There were, however, certain criteria which had to be met:

a) Patients had to have had a minimum of 48 hrs bowel rest with or without total parenteral nutrition (TPN), prior to the commencement of enteral feeding. This period was chosen so that nutrients taken orally prior to the commencement of the trial could be excluded as a cause of diarrhoea.

b) Enteral feeding would only be commenced with the permission of the doctor in charge and would be withdrawn if necessary according to his/her advice.

c) The route of feeding had to be nasogastric rather than via gastrostomy or jejunostomy. Feeds were to be administered at a constant rate of infusion.

d) No other form of enteral nutrition except the enteral feed was to be administered during the trial period.

e) In the final analysis only patients who had been enterally tube fed for a minimum of three days would be included. Three days was chosen as the minimum period so that tolerance of up to 2000ml of feed per 24 hours could be assessed.

Prior to commencement of trial, note was made of the following:

a) A detailed medical history

b) All medication: type, dose and frequency received by the patient for two weeks prior to the start of trial.

c) Type of nutrition received and length of bowel rest before commencement of enteral feeding.

d) Overall condition of the patient including presence of sepsis in association with pyrexia. Patients were considered septic if either blood, sputum or wound cultures were found to be positive.

e) Presence and severity of diarrhoea if present before enteral feeding.

The following were also measured in order to estimate nutritional status:

a) The concentrations of serum albumin, iron, zinc and magnesium.

b) Triceps skinfold thickness and mid upper muscle circumference(MUMC).

Patients

Sixty patients fulfilled the requirements for inclusion in this study. However, enteral feeding was withdrawn in twelve of these patients within 24 hours of commencement. The feeding was stopped at the request of the doctor-in-charge due to medical reasons such as sudden deterioration in clinical condition necessitating a change to TPN, or rapid improvement in clinical condition necessitating a change to an oral diet and transfer from the intensive care unit. The remaining forty eight patients completed the minimum three days of enteral feeding. Fifteen of these 48 patients were females and 23 were males. Seventeen were white, 19 coloured and 12 black. The ages varied from 18 to 84 years and the mean age was 47.5 ± 17.9 years. The mean length of time on enteral feeding was 10.2 ± 11.7 days (range 3 to 56 days). Twenty nine patients

had received treatment in the surgical intensive care and 19 in the respiratory intensive care. A summary of the clinical diagnoses of the patients studied is shown in Table 3.1. Details for each patient may be found in Appendix 1 and details of diagnosis, clinical condition and medication administered may be found in Appendix 2.

Table 3.1 CLINICAL DIAGNOSES OF PATIENTS STUDIED

Diagnosis	Number
Trauma	**17**
Respiratory	**10**
Septicaemia	**5**
Liver failure	**3**
Gastrointestinal	**6**
Abdominal aortic aneurism	**5**
Neurological	**1**
Burns	**1**

2. FEEDS AND FEEDING METHODS

(a) Choice of feeds

Two feeds were chosen for comparison. As a result of the controversy surrounding home-made versus commercial feeds and their association with diarrhoea as well as the untested reputation of Casilan Oil in curtailing diarrhoea, it was decided to compare Ensure (commercial) to Casilan Oil (home-made).

b) Composition and preparation of feeds

Ensure (Abbott Laboratories, Johannesburg, South Africa), a commercially available, lactose free feed, has been the primary source of enteral nutrition in our intensive care units for some time. The home made feed, Casilan Oil, was designed at Groote Schuur Hospital. It contains Casilan powder (Glaxo Laboratories, South Africa) as the protein source, Sunflower oil as the fat source and Caloreen powder (Roussel Laboratories, South Africa) as the carbohydrate source. Multivitamin syrup (Lennon Ltd, Cape Town, South Africa), iron in the form of ferrous gluconate (Fisons Pharmaceuticals, Chloorkop, South Africa), magnesium in the form of magnesium glycerophosphate (Labethica, Bethlehem, South Africa), zinc in the form of zinc sulphate (Groote Schuur Hospital, Cape Town, South Africa), sodium as sodium chloride (Sabax, Johannesburg, South Africa) and potassium as potassium chloride(Labethica, Bethlehem, South Africa) were also added to the Casilan Oil.

Table 3.2 shows the comparative composition of the two feeds.

Table 3.2: NUTRITIONAL ANALYSIS OF ENSURE AND CASILAN OIL

	Ensure	Casilan oil
Type of feed	**Commercial**	**Home-made**
Total kcal/L(non N)	**825**	**840**
Protein content(g/L)	**34**	**45**
N content(g/L)	**5.3**	**7.2**
CHO Content(g/L)	**131**	**120**
Fat content(g/L)	**34**	**40**
Magnesium(mmol/L)	**197**	**190**
Zinc(mg/L)	**15**	**15**
Iron(mg/L)	**9**	**9**
Lactose content(g/L)	**0**	**0**
Osmolality(mOsm/L)	**441**	**383**
Protein Source	**soya protein and casein**	**casein**
Fat Source	**corn oil**	**sunflower oil**
CHO Source	**corn starch**	**glucose polymers**

kcal = kilocalories, N = nitrogen, non N = non nitrogen, CHO = carbohydrate

Both feeds are lactose free. In both the protein source is primarily casein and vegetable oil is the source of fat. Casilan Oil contains slightly more fat than Ensure.

Casilan Oil has a lower osmolality than Ensure primarily because the carbohydrate source consists of glucose polymers rather than simple glucose. The only other major difference between the feeds is that Casilan Oil has a higher protein content.

The recommended daily intake of protein for hypercatabolic critically ill patients is 2.25 g/kg/day which is equivalent to 135 g/day for an individual weighing 60 kg. This is far in excess of the 68 g/day that would be provided by 2000ml of Ensure or even the 90g/day provided by 2000ml of Casilan Oil. Protein would

have to be added to both these feeds so that the nutritional requirements of critically ill patients may be optimally met.

There were two reasons why the quantity of enteral feed given was not according to estimated requirement levels. It has been the policy of the I.C.U to start enterally fed patients on 1000 ml of feed/24 hours and to slowly increase this to 2000 ml/ 24 hours, depending on tolerance. For the purposes of this study, we did not change the method used except that patients were given 2000 ml/ 24 hours by the second or third day after commencement of feeding rather than increased strength of feed over a prolonged period. Secondly, it was primarily tolerance to the feed which we wanted to evaluate, and all patients were therefore prescribed equivalent concentrations and volumes.

The feeds were reconstituted in the diet kitchen during the morning of the day on which they were to be administered. The solutions were mixed in a liquidiser using a non sterile technique and tap water. The solutions were then decanted into 1000ml glass bottles which were transported to the wards and refrigerated until required. The first bottle of feed was started approximately 4 hours after reconstitution. The feed was therefore cold to begin with but soon equilibrated to room temperature.

(c) Technique of administration

All the patients were fed continuously using wide bore Ryle's tubes (16 French). In the majority of cases, the infusion rate was controlled using an infusion pump. The initial rate of infusion was approximately 40 ml per hour and this was increased to 80 ml per hour when the feed was increased to 2000ml per day.

The mean amount of feed administered on the three days to the group who developed diarrhoea after commencement of feeding and the group who did not, is documented in Table 3.3 below.

Table 3.3 Mean amount of feed actually administered for the first three days (Mean ± S.D)

	With diarrhoea (n = 10)	No diarrhoea (n = 38)
Day 1(ml)	**950.0 ± 158.1**	**977.0 ± 86.0**
Day 2(ml)	**1066.7 ± 632.0**	**1461.8 ± 458.2**
Day 3(ml)	**1742.9 ± 250.7**	**1479.0 ± 528.5**

3. PROCEDURE

Patients who fulfilled the criteria for inclusion were randomised to receive either Ensure or Casilan Oil starting on 1000ml full strength feed for the first 24 hrs. This was increased from day 2 onwards according to the patient's fluid requirements. Twenty seven patients received Ensure and 21 received Casilan Oil.

(a) Assessment of tolerance to enteral feed

Tolerance was assessed mainly by the presence or absence of diarrhoea. However, other symptoms of intolerance such as vomiting or abdominal distension were also noted if present. Diarrhoea was defined as mild (< 3 loose stools per day), moderate (3 - 5 loose stools per day) and severe (greater than 5 loose stools per day). If patients developed severe diarrhoea, they were crossed over to receive the alternative feed.

(b) Assessment of clinical condition

During the study note was made concerning medication administered and overall medical condition of the patient. In addition, serum levels of albumin were measured every day. In patients who had diarrhoea stool samples were cultured to test for the presence of infectious organisms. Samples of the feeds were examined for contamination on each day of the trial. Small intestinal bacterial overgrowth was tested for in twenty six of the patients on the third day after commencement of enteral feeding, using the 1g ^{14}C xylose breath test[66].

4. METHODS

(a) Estimation of nutritional status

The methods of Blackburn and Thornton[165] were used for assessment of anthropometric measurements. All anthropometric measurements were taken by the author, ensuring good reproducibility. Each measurement was taken three times and the final result obtained by averaging the two closest values.

Triceps skinfold thickness

Fat stores were estimated by measurement of the triceps skinfold thickness. Triceps skinfold thickness is a measure of the patient's subcutaneous fat stores and is considered to be a good index of overall body fatness[152]. The measurement was made using Harpenden calipers. The width of a fold of skin on the triceps muscle halfway between the acromial process of the scapula and the olecranon process of the ulna is measured. By comparing the measurement to standard values it is possible to calculate the "percentage of normal". In this way fat stores can be estimated.

Mid upper arm circumference (MUAC)

The mid upper arm circumference is the circumference of the upper arm at the same point at which the triceps skinfold thickness is measured.

Mid upper muscle circumference (MUMC)

Mid upper muscle circumference gives an estimation of muscle size and is calculated using the triceps skinfold and MUAC measurements in the formula:

MUMC(cm) = MUAC(cm) - (3.14 x triceps skinfold thickness(cm))

The value obtained is then compared to standard values[153].

Weight was not measured as in addition to being extremely difficult to obtain a weight measurement in these critically ill patients most of whom are intubated and heavily sedated, the results are often not accurate due to the fluctuations in fluid balance which commonly occur.

Serum levels of iron, zinc and magnesium were obtained as part of the nutritional assessment.

(b) Bacteriology

Feed samples were tested for bacterial contamination for the first three days of feeding, approximately 24 hrs after reconstitution. Samples were taken from the bottle while the feed was being administered to the patient. The rubber stopper of the bottle was wiped with an alcohol swab and samples were drawn into sterile syringes. These were then immediately taken to the Bacteriology laboratory for culturing as follows. Sterile 1 ml pipettes were used to transfer samples. 0.1 ml of the feed sample was plated onto 4% blood agar. Another 0.1 ml sample was mixed with 9.9 ml sterile Difco Nutrient Broth (D.N.B) to facilitate counting. 0.1 ml of this solution was also plated onto 4% blood agar. The remainder of the feed sample was then centrifuged, the supernatant discarded and the deposit plated onto 2% blood agar in a McConkey plate to test for gram -ve single colonies. All plates were then incubated overnight before organisms were identified and reported as colony forming units(cfu)/ml.

(c) Small intestinal bacterial overgrowth

Detection

The conventional method of detecting bacterial overgrowth is by bacteriologic culture from jejunal aspirates[61,62]. However in addition to being an invasive procedure, the collection and culture of specimens is complicated and time consuming.

A number of alternative methods are available for evaluation of bacterial overgrowth. Urinary indican excretion has been used to test for the presence of bacterial overgrowth[154] but can neither accurately identify the site of overgrowth nor differentiate between bacterial overgrowth and other malabsorption disorders[61]. Several other diagnostic procedures have been evaluated. These methods rely on metabolism by the bacteria of ingested substrates such as ^{14}C labelled bile acids[155], ^{14}C-d-xylose[156] or carbohydrate[157]. The measurement at timed intervals of the breath excretion of labelled ^{14}C carbon dioxide or hydrogen liberated from the substrate by the bacteria gives an indication of the presence and concentration of the bacteria.

The ^{14}C-d-xylose method used by Toskes and King has been shown to be the most sensitive and specific of those mentioned above and is a reliable test for detection of small bowel bacterial overgrowth[66,158,159]. In the normal healthy person a test dose of ^{14}C xylose would be absorbed intact in the jejunum and be excreted unchanged in the urine as it cannot be metabolised by man. In the presence of small intestinal bacterial overgrowth, however, the ^{14}C xylose is metabolised. Oxidation results in the production of ^{14}C carbon dioxide and water which are absorbed into the bloodstream. The ^{14}C carbon dioxide is then excreted in expired breath. Consequently, detection of ^{14}C-labelled carbon dioxide in the breath provides an indirect measure of bacterial overgrowth. It is, however, important to note that the small bowel is not entirely sterile and contains a light bacterial growth. Therefore, even in the normal individual, a small amount of ^{14}C xylose is oxidised to ^{14}C carbon dioxide. An increase in excretion of ^{14}C carbon dioxide would indicate bacterial overgrowth whereas reduced excretion of label could represent either abnormally suppressed bacterial flora or reduced intestinal motility.

A modified version of the method used by Toskes and King[156] was used in the present study. 5μCi of labelled xylose was given rather than the 10μCi used by Toskes and King as this dose was found to yield sufficient $^{14}CO_2$ for reproducible measurements. The dose has the added advantage of halving the radiation exposure. The length of time for which patients were fasted was less than the usual 10 hrs as they were receiving continuous drip feeding. The infusion of enteral feed was stopped 4 hours before the ingestion of the xylose.

Preparation of dose

In order to minimize the possibility of bacterial contamination, a solution of labelled xylose was made by mixing 500 ml of sterile water with 250μCi of ^{14}C-xylose(Amersham, U.K)). This was then divided into 10 ml aliquots which were bottled and stored at -16 C until required. The 10ml of labelled solution was thawed prior to the test and mixed with 1g of non-labelled d-xylose (Saarchem Pty Ltd, Muldersdrift, South Africa).

Clinical Method

Sixty ml of distilled water was added to the labelled solution and this mixture was then given as a bolus to the patient, via the nasogastric tube and flushed down the tube with a further 60ml of water. Breath samples were collected in 2L douglas bags before the test and at half hour intervals for 3 hours following ingestion of the xylose. These were taken either directly from the patient or if the patient was receiving ventilatory support, from the expiratory port of the ventilator. One mmol of CO2 was trapped by bubbling the breath sample into a solution containing 1 mmol hyamine hydroxide(Packard Instruments, Groningen, Netherlands) and phenolphthalein indicator(Merck, Darmstadt, Germany). Ten ml scintillation mixture (Instagel, Packard Instrument Co, Downer's Grove, Illinois, U.S.A) was then added and the activity (expressed as dpm (disintegrations per minute)) of the mixture was measured by liquid scintillation counting using the Tri-carb 1500 liquid scintillation counter (Packard Instrument Co, Downer's Grove, Illinois,U.S.A). The activity measured by the counter gives an indication of the proportion of orally ingested 14C xylose expired as 14CO2 per mmol CO2.

Calculation of results

The pre-dose dpm measurement was taken as a baseline background count and was therefore subtracted from the total dpm obtained for the subsequent samples. Results were calculated according to the formula:

$$\%\ \text{of ingested } {}^{14}\text{C xylose excreted as } {}^{14}\text{C}0_2 = \frac{\text{dpm in 1 mmol expired } CO_2}{\text{dpm in } 5\mu\text{Ci } {}^{14}\text{C-xylose}} \times 100$$

and the percentages plotted against time.

(d) Stool cultures

Stool samples were tested for the presence of pathogens such as shigella and salmonella using a FPC (Fecal Parasite Concentrator)(Evergreen Scientific, U.S.A).

5. ANALYSIS OF DATA

Data was analysed using an IBM AT computer. A database (DBASE III) was used for most of the analysis. A statistical package (EPISTAT) was used for statistical analysis.

The CHI-square test was used to assess the significance of differences in the relative frequencies of discrete variables. This test was used to assess the significance of the difference between the number in the group who had diarrhoea compared to the number in the group who did not, concerning the various factors possibly associated with diarrhoea. As the number of patients in this study was small, if the number of patients was less than 5 in any cell, the Fisher's exact test was used instead of the CHI- square.

The unpaired Student's t-test was used to assess the significance of differences between the means in groups when a certain parameter was measured for each patient and a mean and standard deviation obtained for the group.

CHAPTER 4

RESULTS

1. INCIDENCE OF DIARRHOEA

Forty eight patients completed at least three days on enteral feeding and thereby became eligible for analysis. Of these 48, 10 patients had had diarrhoea before the commencement of enteral feeding and 10 developed diarrhoea after enteral feeding was started. The incidence of diarrhoea either with or without enteral feeding was therefore 42% (20/48). Diarrhoea continued in four of the ten patients who had passed loose stools before enteral feeding and settled in the remaining six just after commencement of feeding. Fourteen patients had diarrhoea whilst receiving enteral feeding. However, as four of these patients had had diarrhoea before feeding was started, a true reflection of incidence of diarrhoea related to enteral feeding would be attained by excluding the entire group of ten patients who had had diarrhoea before the start of enteral feeding. Diarrhoea could therefore have been attributed to enteral feeding in only 10/38 (26%) (Fig 4.1).

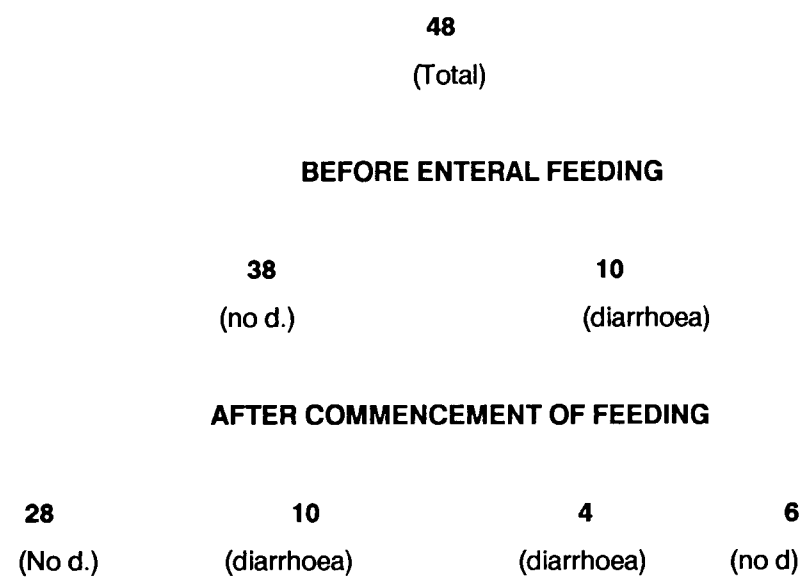

Fig.4.1 Incidence of diarrhoea before and after enteral feeding (d = diarrhoea)

2. ANALYSIS OF TOLERANCE

(a) Diarrhoea before feeding

Of the 10 patients who had had diarrhoea before enteral feeding commenced, 5 patients had mild diarrhoea and 5 had moderate diarrhoea. In 6 of these patients, the diarrhoea resolved within 24 to 48 hours of the commencement of feeding. The remaining 4 patients continued having diarrhoea of the same severity. (Figure 4.2).

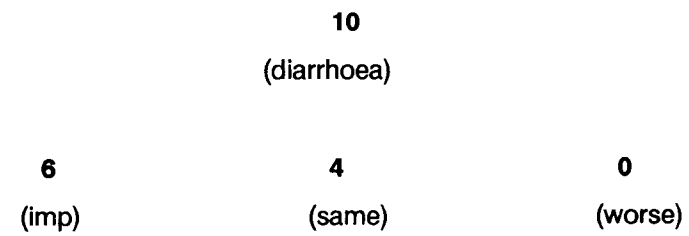

Fig. 4.2 Follow-up of diarrhoea after commencement of enteral feeding in patients who had had diarrhoea before. (Imp = improved)

(b) Diarrhoea after feeding

Of the group of 10 patients who developed diarrhoea after commencement of enteral feeding, figure 4.3 demonstrates that the majority experienced mild episodes.

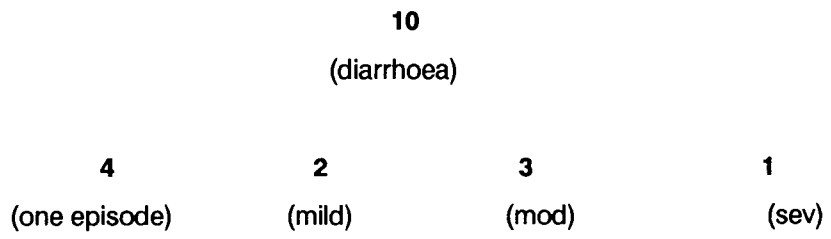

Fig 4.3. Severity of diarrhoea experienced by patients who developed diarrhoea after commencement of enteral feeding. (mod = moderate, sev = severe).

Four of these patients experienced only one episode of mild diarrhoea on the third day after enteral feeding had started and none thereafter. Five patients developed mild to moderate diarrhoea within 48 hours of commencement of feeding which continued for at least three days before improving and 1 patient developed severe diarrhoea (>8 loose stools per day) which continued for one week.

(c) Other side effects

Concerning other side effects, 2 patients who had no diarrhoea developed abdominal distension, and two patients who had diarrhoea also had an episode of vomiting.

(d) Additional observations

No significant difference was noted in the mean age of the group of 20 who had diarrhoea compared to the group of 28 who did not. The mean age for the non-diarrhoea group was 47.3 ± 17.6 years and for the diarrhoea group, 48.8 ± 18.7 years. Table 4.1 shows that race did not correlate with the occurrence of diarrhoea but that significantly more females had diarrhoea than males. In addition, significantly more patients who had diarrhoea (85%) were in the surgical intensive care units than in the respiratory I.C.U's ($p < 0.05$).

Table 4.1 Relationship of race,sex and type of I.C.U to occurrence of diarrhoea

	Diarrhoea (n = 20)	No diarrhoea (n = 28)	p
Males	**10**	**23**	**0.04**
Females	**10**	**5**	**(CHI^2)**
Whites	**8**	**9**	**0.76**
Coloureds	**8**	**11**	**(CHI^2)**
Blacks	**4**	**8**	
Surgical ICU	**17**	**15**	**0.049**
Respiratory ICU	**3**	**13**	**(F.E)**

F.E = Fisher's Exact test

3. POSSIBLE CAUSES OF DIARRHOEA

All the patients who had diarrhoea, either before or after the commencement of enteral feeding, were investigated as to the possible causes of the diarrhoea.

a) Disease

Details of primary diagnoses and clinical features of the patients are given in Appendix 2. Of the 20 patients who had diarrhoea either before or during the study period, the diarrhoea which developed could have been due to disease in 6 patients. Patients 9 and 20 had undergone gastrectomies just prior to going on the trial. Patient 1 had had a colectomy. Patient 11, who developed severe diarrhoea at the start of feeding, had bowel ischaemia after abdominal and chest trauma. Patient 12 had acute haemmorrhagic pancreatitis. Patient 13 had developed an abdominal abscess.

Fifteen of the 20 patients who had diarrhoea had experienced some form of abdominal injury, including surgery, compared to 11 of the 28 who had no

diarrhoea. Abdominal injury due to either trauma or surgery significantly correlated with the occurrence of diarrhoea (p = 0.03).

b) Factors relating to clinical condition

Table 4.2 summarises the data pertaining to clinical factors in the aetiology of diarrhoea.

Table 4.2. Clinical factors and occurrence of diarrhoea

	Diarrhoea (n = 20)	No diarrhoea (n = 28)	Total (n = 48)	p
Sepsis	**10**	**16**	**26**	**0.84(CHI^2)**
Albumin < 26g/l	**5**	**4**	**9**	**0.57(F.E)**
Lngth BR> 7 days	**2**	**1**	**3**	**0.37(F.E)**

Lngth BR = days of bowel rest prior to feeding, F.E = Fisher's Exact test

None of the above factors significantly correlated with the occurrence of diarrhoea. In addition none of the stools tested contained pathogenic organisms. Uremia was not present in any of the patients with diarrhoea.

c) Nutritional status

Table 4.3 summarizes the anthropometric and trace element measurements. The Student's t-test was used to compare the means of the values measured in the two groups.

Table 4.3. Nutritional status versus occurrence of diarrhoea

	Diarrhoea	No diarrhoea	p
% ideal MUMC	**96.1± 13.5**	**97.5± 16.1**	**0.9**
% ideal triceps	**70.6± 23.0**	**84.2± 48.6**	**0.4**
Zinc(mmol/L) n (8.4 - 22.9)	**10.9 ± 5.0**	**11.2 ± 2.8**	**0.1**
Mg(mmol/L) n (0.7 - 1)	**0.79 ± 0.2**	**0.87 ± 0.2**	**0.8**
Iron(mmol/L) n (8 - 30)	**9.10 ± 7.1**	**5.00 ± 4.3**	**0.2**

Mg = magnesium, n = normal range

Nutritional status was similar in the two groups. There were no patients who were severely nutritionally depleted. Serum levels of zinc and magnesium were within normal ranges in the majority of patients but serum iron levels were lower than normal in the group of patient who did not have diarrhoea.

d) Medication

Details of medication administered to the patients may be found in Appendix 2.

Antibiotics

Table 4.4 is a list of the most commonly administered antibiotics and their association with the occurrence of diarrhoea. Most of the antibiotics were intravenously administered.

Table 4.4 Relationship of antibiotic treatment to occurrence of diarrhoea

	Diarrhoea (n = 20)	No diarrhoea (n =28)	Total (n = 48)	p
General	**16**	**25**	**41**	**0.63 CHI^2**
***Amikacin**	**14**	**10**	**24**	**0.04 CHI^2**
Flagyl	**6**	**9**	**15**	**0.87 CHI^2**
PenG	**7**	**7**	**14**	**0.67 CHI^2**
Cloxacillin	**2**	**6**	**8**	**0.26 F.E**

*** = $p < 0.05$**

F.E = Fisher's Exact test

Although antibiotic treatment in general was not related to diarrhoea, treatment with the antibiotic, amikacin (500 mg/day i.v) was significantly associated with the occurrence of diarrhoea ($p<0.05$). The validity of this significance was, however, questioned. In view of the association noted between diarrhoea and abdominal injury, the correlation between abdominal injury and amikacin was examined.

Of the total of 48 patients studied, 32 had either abdominal injury or amikacin or both. Fifty five per cent (18/32) of patients who had one or other or both of the above, had diarrhoea. In contrast only 12,5% (2/16) of patients who had neither abdominal injury or amikacin, developed diarrhoea (Table 4.5).

Table 4.5 Association between amikacin therapy, abdominal trauma and the occurrence of diarrhoea.

	Diarrhoea	No diarrhoea
+amikacin +abd. injury	**11**	**6**
+amikacin -abd. injury	**3**	**4**
-amikacin +abd. injury	**4**	**4**
-amikacin -abd. injury	**2**	**14**

abd. trauma = abdominal trauma

Of the twenty patients with diarrhoea, 4 had abdominal injury alone and 3 had amikacin alone whereas 11 had both abdominal injury and amikacin. The occurrence of diarrhoea differed significantly in the group who had both amikacin and abdominal injury compared to those who had either amikacin ($p = 0.009$) or abdominal injury ($p = 0.024$). This would suggest that the combination of the two factors increased the occurrence of diarrhoea, but that it is not possible to determine which was of greater significance.

Anti-ulcer therapy

Table 4.6 lists the number of patients who received agents for the prevention of stress ulceration.

Table 4.6 Agents used to prevent stress ulcers

Anti-ulcer drug	Diarrhoea (n = 20)	No diarrhoea (n = 28)	Total (n = 48)
Sucralfate	**12**	**9**	**21**
Ranitidine	**1**	**3**	**4**
No anti-ulcer drug	**7**	**16**	**23**

Oral sucralfate (1g QID) (Continental Ethicals, Cape Town, South Africa) was used in twenty one patients and the H_2 receptor antagonist, ranitidine (50mg I.V) (Glaxo, Wadeville, South Africa) in four.

The use of sucralfate or ranitidine was not positively associated with diarrhoea ($p = 0.45$).

Lactulose

Three patients (patients 4,8 and 14) were given lactulose as treatment for liver failure. All three had diarrhoea.

e) Small intestinal bacterial overgrowth

Twenty six patients were tested for the presence of small intestinal bacterial overgrowth using the ^{14}C xylose test.

^{14}C xylose excretion results obtained for the I.C.U patients in this study were compared to those previously obtained in our laboratory in normal control subjects and in patients with known bacterial overgrowth[160]. The results obtained for these patients were similar to those of Toskes and King for comparable groups[156].

In the following graphs relating to the results of the xylose breath test, the percentage of ingested ^{14}C xylose expired as $^{14}CO_2$ is plotted against time after ingestion. The Student's t-test was used to assess the significance of differences.

Only one patient excreted significantly more $^{14}CO_2$ than controls, indicative of bacterial overgrowth. This patient developed mild diarrhoea within 24 hours of the start of enteral feeding. After three days on enteral feeding the patient was given a normal ward diet as he had been extubated and could eat normally. The mild diarrhoea, however, continued.

Fig. 4.4 illustrates that the patient's curve of excretion of $^{14}CO_2$ over the three hour period was markedly elevated.

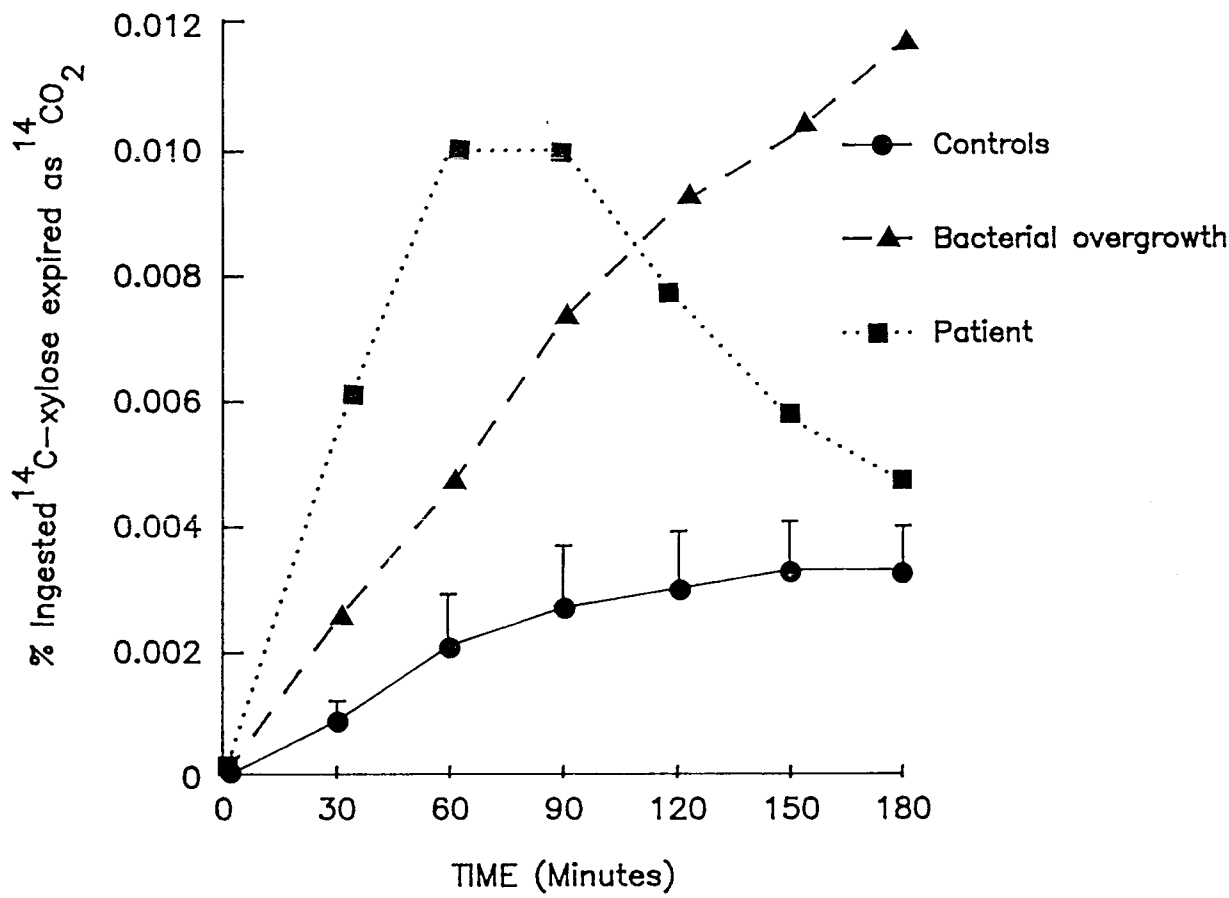

Fig. 4.4 Metabolism of ^{14}C xylose in patient with positive bacterial overgrowth

Fig 4.5 illustrates that the entire group of 26 patients studied excreted significantly less $^{14}CO_2$ than controls. All of these patients were receiving or had recently received some form of antibiotic therapy.

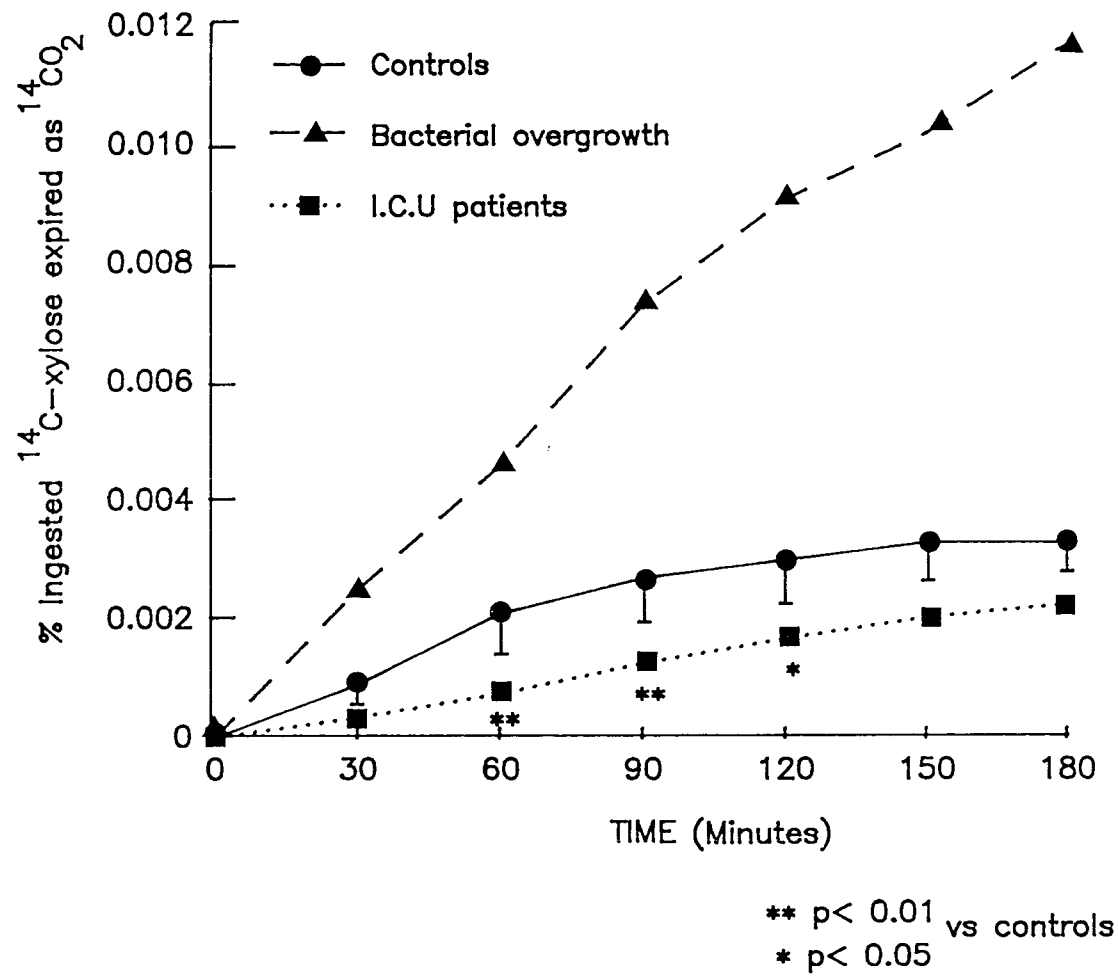

Fig. 4.5 Metabolism of ^{14}C xylose in critically ill patients (Mean ± S.D)

The effect of various factors on the metabolism of ^{14}C xylose was then investigated.

The results of the bacterial overgrowth studies with particular reference to the occurrence of diarrhoea are shown in Figure 4.6.

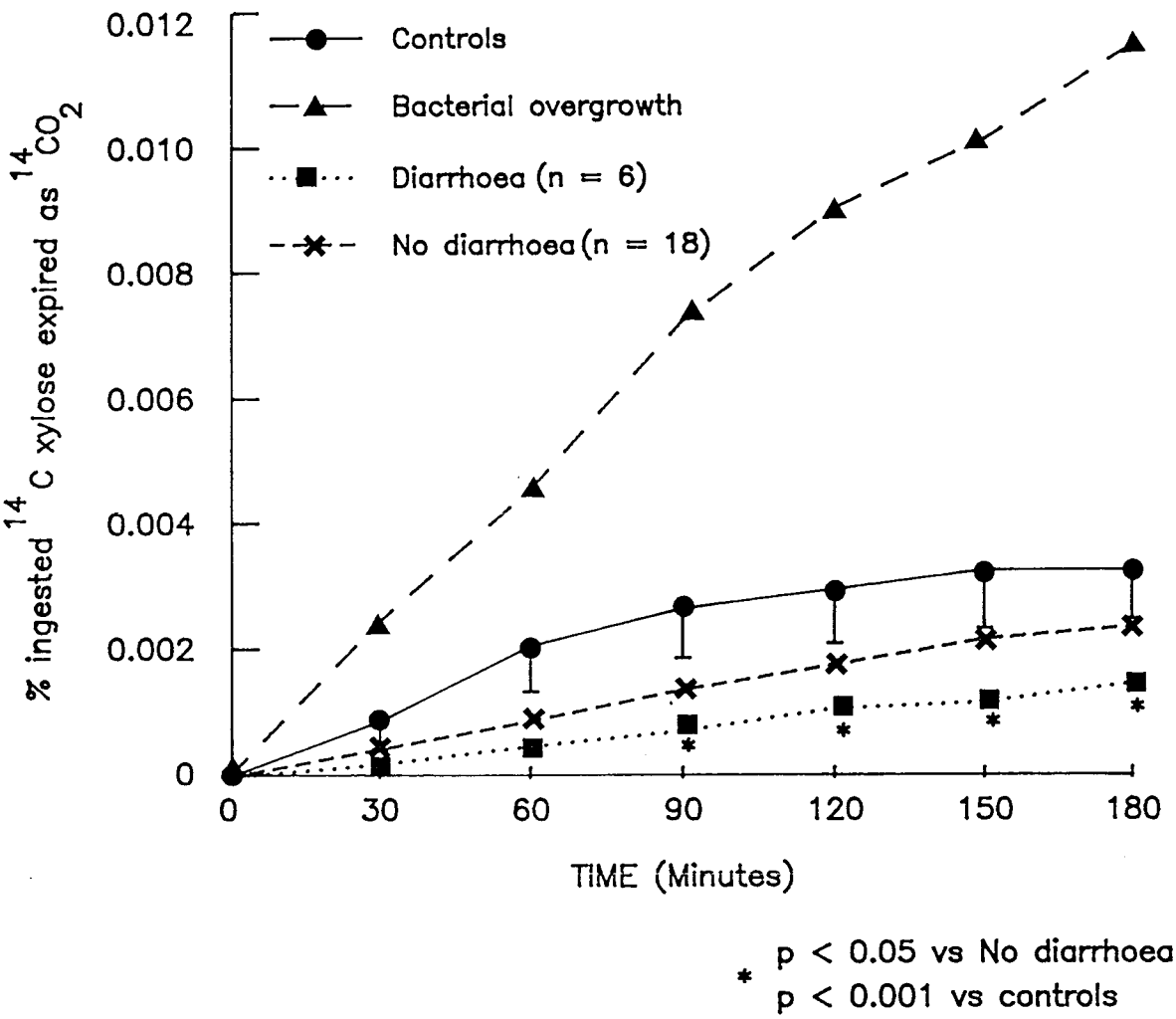

Fig 4.6 Metabolism of ^{14}C xylose in patients with and without diarrhoea (Mean ± S.D)

Patients who had diarrhoea when the ^{14}C xylose test was done, excreted significantly lower amounts of $^{14}CO_2$ than those who had no diarrhoea at the time of the test.

In view of the association between amikacin therapy and the occurrence of diarrhoea (Table 4.4) and the possible association between antibiotic therapy and alteration of the bowel flora we investigated the effect of amikacin on the metabolism of ^{14}C xylose (Figure 4.7).

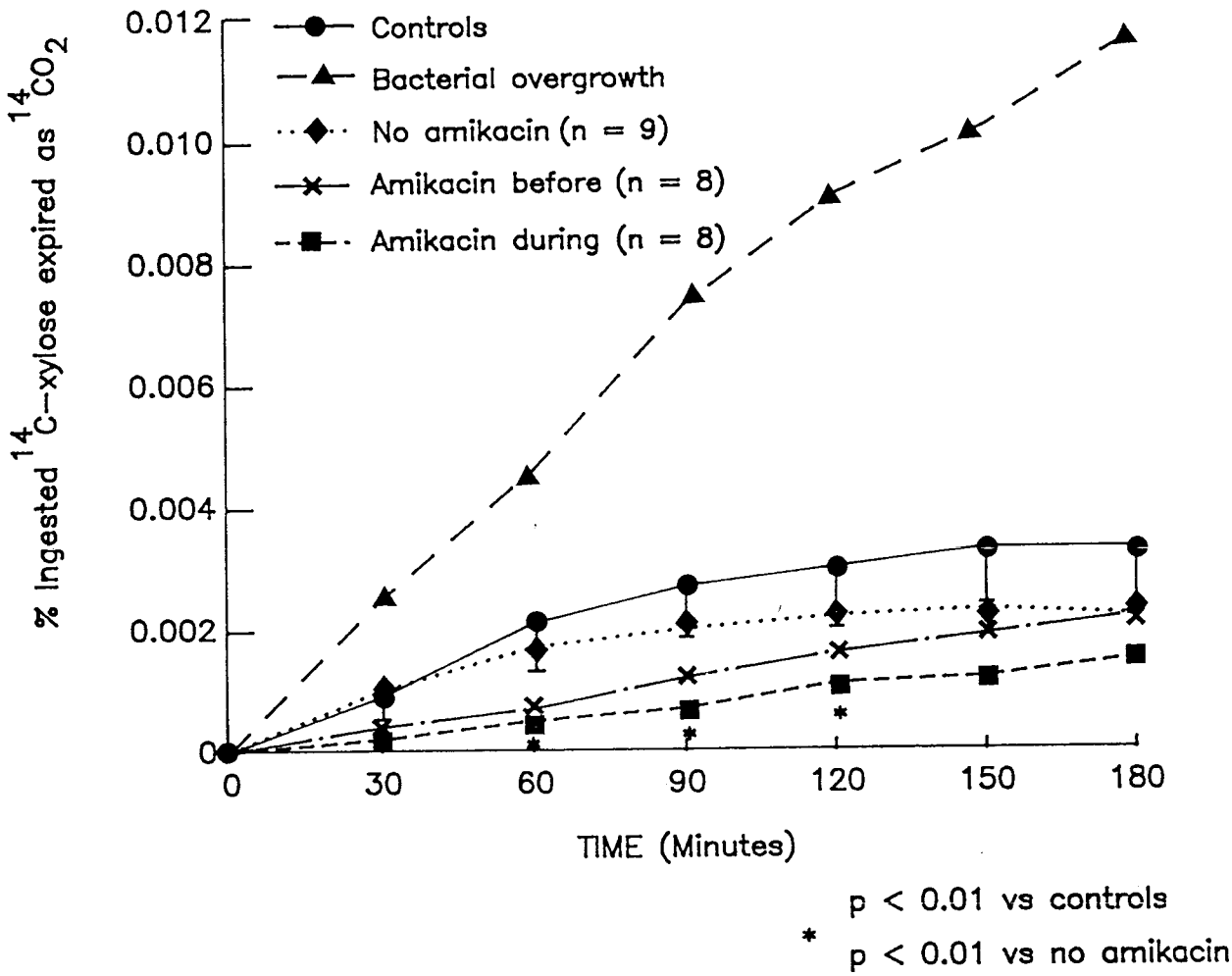

Fig 4.7 Metabolism of ^{14}C xylose in patients receiving amikacin therapy (Mean ± S.D)

Patients who were receiving amikacin therapy at the time of the bacterial overgrowth test excreted significantly lower amounts of $^{14}CO_2$ than patients who had not been on amikacin ($p < 0.05$). $^{14}CO_2$ excretion in the group who had not received amikacin therapy was similar to that found in controls. The group of patients who had received amikacin in the period prior to the study excreted intermediate amounts of $^{14}CO_2$.

Further analysis of the bacterial overgrowth test with regard to anti-ulcer therapy showed that there was no significant difference in the excretion of $^{14}CO_2$ between patients who received treatment with sucralfate and those who received no treatment for possible stress ulceration (Figure 4.8).

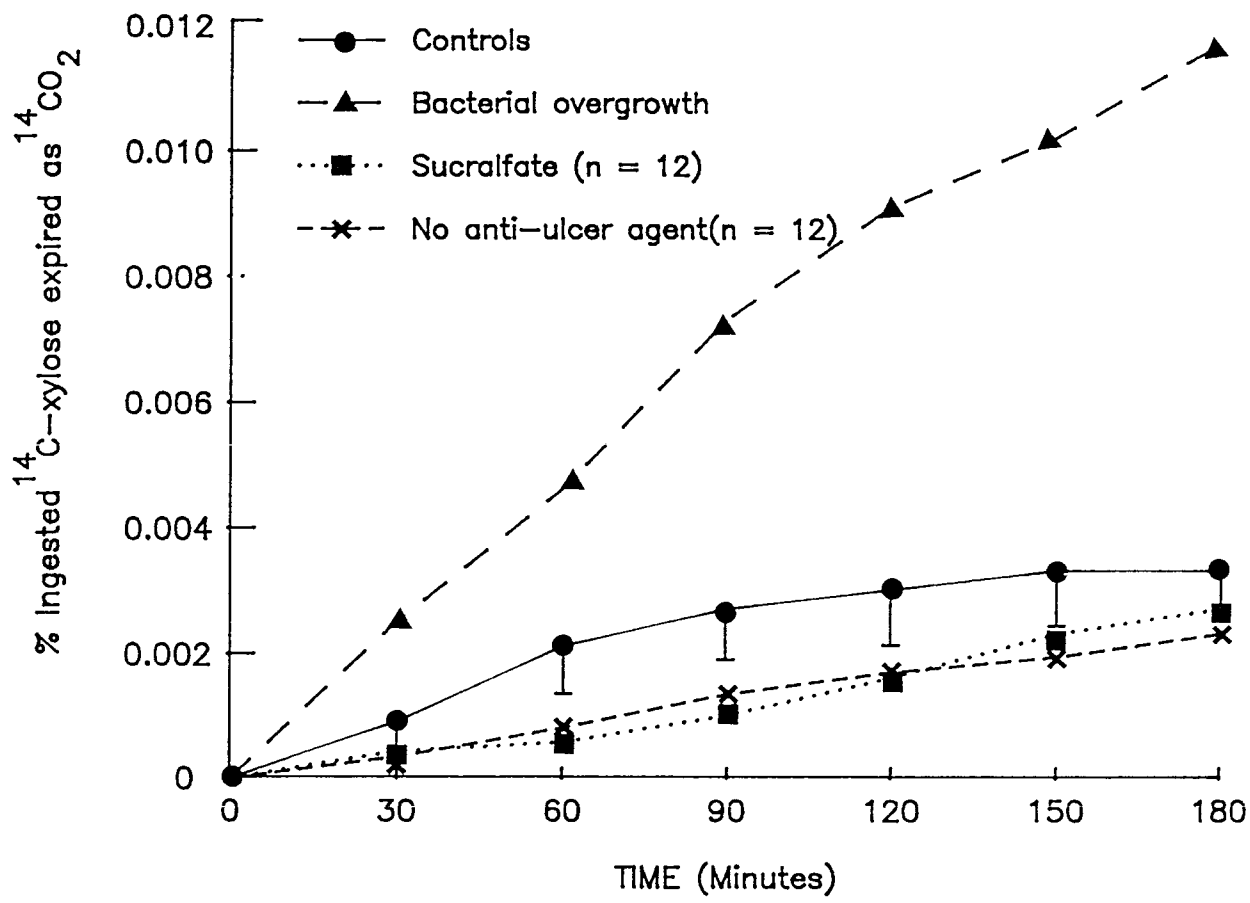

Fig 4.8. Relationship between metabolism of ^{14}C xylose and sucralfate therapy (Mean ± S.D)

g) Enteral feeding

Diarrhoea developed in 10 of the 48 patients when enteral feeding was commenced. Factors other than enteral feeding could, however, have caused the diarrhoea in seven of the ten. Patient 20 had had had a gastrectomy, patient 11 had severe ischaemia, patient 12 had acute pancreatitis, patient 14 had been receiving lactulose as treatment for liver failure, patient 19 tested positive for bacterial overgrowth, patient 13 had an abdominal abscess and patient 18 had suffered severe abdominal trauma. No direct cause could be found for the mild diarrhoea which developed in the remaining three patients.

The choice of feeds and method of administration used for this study eliminated lactose intolerance, hyperosmolality, fat, and temperature of the feed as potential causes of diarrhoea.

Type of feed

Table 4.7 lists the number of patients who received Ensure or Casilan Oil. Diarrhoea was as common in patients who received Ensure as in those who received Casilan Oil($p = 0.89$).

Table 4.7 Ensure versus Casilan Oil

	With diarr. (n=10)	No diarr. (n=38)	Total (n=48)
Ensure	**6**	**19**	**25**
Casilan Oil	**4**	**15**	**19**

Contamination of feeds

All samples of the feeds given to patients in this study contained more that 2×10^5 cfu/ml. This is far in excess of the 200 cfu/ml which is the maximum acceptable in reconstituted enteral feeds[116]. However, as every patient did not develop diarrhoea when given the contaminated feed, contamination was not directly associated with diarrhoea.

Table 4.8 is a comparison of the various organisms which were cultured in the feed samples taken from both the diarrhoea group and the non-diarrhoea group. The numbers given represent the percentage of patients in each group who received a feed during the study period which contained the particular organism. The CHI-square test was used to assess the significance of differences.

Table 4.8 Frequency of occurrence of organisms in the feed samples

Type of organism	Diarrhoea (%)	No diarrhoea (%)	p
Klebsiella sp	**80**	**88**	**0.94**
Enterobacter	**50**	**67**	**0.67**
Bacillus sp	**50**	**63**	**0.83**
Alpha strep.	**60**	**30**	**0.17**
Staph. epi.	**50**	**37**	**0.68**
E. coli	**50**	**33**	**0.53**
Citrobacter	**30**	**8**	**0.20**
Staph. aureus	**10**	**0**	**0.59**

Alpha strep = alpha haemolytic streptococcus, Staph epi = staphylococcus epidermidis, E coli = escherichia coli, Staph aureus = staphylococcus aureus, sp = species

There was no significant difference in the type of organisms found in the samples of feeds given to the patients who had diarrhoea compared to those who did not. In addition there was no difference in the degree of contamination between the Ensure and the Casilan Oil.

No factor relating to the composition of the feeds was significantly associated with diarrhoea.

4. TREATMENT OF DIARRHOEA

Only one patient (patient 11) developed severe diarrhoea while on enteral feeding. This patient was commenced on enteral feeding with Casilan Oil. The feed was changed to Ensure after 48 hours but the diarrhoea continued as before for a further two days. Enteral feeding was then discontinued for 24 hours and the patient was treated with codeine phosphate (30g orally, 6 hourly). The diarrhoea improved and enteral feeding was successfully re-introduced.

Patient 12, who had severe acute pancreatitis had moderate diarrhoea on both Ensure and Casilan Oil, but when a special low fat feed containing medium chain triglycerides was introduced, the diarrhoea improved.

No other patients were crossed over to the alternative feed. The mild to moderate diarrhoea which developed at the start of enteral feeding in the remaining eight patients improved within two to five days without any intervention.

5. EFFECT OF DIARRHOEA ON LENGTH OF STAY IN ICU AND OUTCOME

The length of time spent in I.C.U by the diarrhoea and non-diarrhoea groups is compared in Table 4.9.

Table 4.9 Effect of diarrhoea on length of stay in intensive care unit

	With diarrhoea (n = 20) (m ± S.D)	No diarrhoea (n = 28) (m ± S.D)
Days in I.C.U	**13.9 ± 7.8**	**19.4 ± 14.0**
Range	**5 - 34**	**4 - 60**

The presence of diarrhoea either before or after the start of enteral feeding did not significantly affect length of stay in intensive care.

Table 4.10 shows the relationship between diarrhoea and the clinical condition of the patients on completion of trial.

Table 4.10. Outcome versus presence of diarrhoea

	Diarrhoea (n = 20)	No diarrhoea (n = 28)	P
Condition improved	**9 (45%)**	**18 (64%)**	**0.30 CHI^2**
Condition unchanged	**6(30%)**	**7 (25%)**	**0.97 CHI^2**
Condition worse	**1 (5%)**	**0 (0%)**	**0.41**
Died	**4 (20%)**	**3 (11%)**	**0.26 F.E**

F.E = Fisher's Exact test

The presence of diarrhoea was not associated with a significantly higher mortality rate.

CHAPTER 5

DISCUSSION

Previous authors have investigated the incidence of diarrhoea among critically ill patients[31,35,49,50]. In the present study, 20 of the 48 (42%) patients who were investigated had diarrhoea, with or without enteral feeding. The incidence of diarrhoea among critically ill patients studied was therefore similar to that reported in previous, albeit not comparable, studies.

If one examines the incidence of diarrhoea related to enteral feeding in particular, of the 20 patients who experienced diarrhoea, ten had had diarrhoea before the commencement of feeding and ten developed diarrhoea after feeding was started. Of the ten who had had diarrhoea before , six settled on enteral feeding and the diarrhoea persisted in the remaining four. Although fourteen patients experienced diarrhoea whilst on enteral feeding, a true reflection of incidence of diarrhoea related to enteral feeding may be obtained by excluding the 10 patients who had had diarrhoea before. Diarrhoea may therefore have been associated with enteral feeding in 26% (10/38) of patients. It is, however, important that the diarrhoea which developed in these 10 patients could have been caused by factors other than enteral feeding in 7 of the 10. The occurrence of diarrhoea among patients receiving enteral feeding was lower than that reported in recent studies by Kelly et al[31], Brinson and Kolts[49] and Gottschlich et al[97] but similar to that found in the earlier studies by Peaston[34], Broome and Jones[65] and Woolfsen et al[35]. It is however notable that the number of patients investigated is small in both the present study and the earlier studies. In contrast, the recent studies utilised far larger groups of patients. This may account for the differences in the prevalence of diarrhoea.

There is considerable controversy concerning the incidence of diarrhoea as related to the type of enteral feed used, in particular, home-made versus commercial. In the present study, we have compared a home-made feed (Casilan Oil) to a commercial feed (Ensure). The composition of the Ensure and Casilan Oil differed with respect to osmolality, carbohydrate source and fat content. As osmotic pressure is affected mainly by the type and quantity of carbohydrate as well as the electrolytes in a feed, Silk et al[139] have

recommended the use of glucose polymers in enteral feeds so that the calories may be increased without increasing the osmolality. The home made feed used in this study is similar to the one used in a study done by Woolfsen et al[35] as both contained glucose polymers as the carbohydrate source and caloreen as the protein source. The home-made feed used in the study by Broome and Jones[65] also contained glucose polymers as the source of carbohydrate. The incidence of tube feed related diarrhoea was low in both these studies and similar to that found in the present study. The use of glucose polymers and the resultant lower osmolality of the Casilan Oil was, however, not associated with a lower incidence of diarrhoea than that noted in patients who received Ensure, where the carbohydrate source was corn starch. Glucose polymers would nevertheless be useful if the calories of a feed had to be increased without increasing the osmolality.

Casilan Oil contained slightly more fat (40g/l) than Ensure (34g/l). Although Gottschlich et al reported that 62% of patients developed diarrhoea when given a feed containing 33g fat/l[138], we found that 34 - 40 g fat per litre of feed was tolerated by the majority of patients on enteral feeding. The diarrhoea which developed in patient 12, who had acute pancreatitis, could have been precipitated by the fat in the feed as improvement was noted when the patient was given a special low fat diet, containing medium chain triglycerides.

Bacterial contamination of the feeds was universal and bacterial counts exceeded 2×10^5 cfu/ml in every sample analysed. A wide variety of organisms was identified. However, there was no direct association between bacterial contamination or the types of bacteria and the incidence of diarrhoea. It has been reported that contamination is more likely in home-made feeds[19]. We have, however, found the degree of contamination to be similar in the Ensure and Casilan Oil.

Although bacterial contamination was not significantly associated with the occurrence of diarrhoea, it is a cause for concern that such high levels of contamination were present in our enteral feeds. Enteral administration of contaminated feeds with possible side effects such as septicaemia[124], cross infection[123] or colonization of the gastrointestinal tract[106] should be avoided at all costs, particularly in critically ill patients who are more prone to developing

infection. It is therefore recommended that the possible source/s of the contamination should be isolated by testing samples of the feed at various stages of preparation and administration.

In spite of the differences in composition between the Ensure and the Casilan Oil, there was no significant difference in the occurrence of diarrhoea on the two feeds. The anecdotal reputation of Casilan Oil as a cure for diarrhoea is therefore not substantiated by the present data.

Home-made feeds were administered in the studies by Peaston[34] , Broome and Jones[65] and Woolfsen et al[35] in which low incidences of tube-feed related diarrhoea were reported. Commercially available products were used in the later studies done by Kelly et al[31], Brinson and Kolts[49] and Gottschlich et al[97] who reported higher incidences. The only controlled study in which a home-made feed was compared to a commercial feed is that by Keighley et al[20]. The authors reported an increased occurrence of diarrhoea in patients receiving a "home-brew" compared to those who were given a commercial preparation. Unfortunately, details of possible causes of diarrhoea other than disease and enteral feeding were not investigated. In addition the feeds used differed to those used in the present study.

No particular factor pertaining to the composition of either of the feeds was significantly associated with diarrhoea. Our findings support the view that "starter regimens" are unnecessary as the majority of patients included in the present study tolerated 1000ml full strength feed at the commencement of feeding. In the ten patients who had had diarrhoea before feeding was commenced, the diarrhoea did not worsen when enteral feeding was started. On the contrary, a marked improvement was noted in six of the ten shortly after feeding was commenced.

Disease could have been a direct cause of diarrhoea in seven of the patients. In addition, abdominal injury was found to be positively associated with diarrhoea. A possible explanation for this association could be based on the hypothesis that shock causes diversion of blood flow from the intestinal mucosa and results in failure to absorb sodium and water from the colon as well as changes to bile acid metabolism[161]. This may in turn induce diarrhoea. The

association between abdominal injury and diarrhoea may have a bearing on the higher occurrence of diarrhoea noted in the surgical intensive care units. The question of a possible association between abdominal injury and diarrhoea has not been investigated in previous studies. There was no obvious clinical cause for the diarrhoea in only three of the patients who developed diarrhoea while on enteral feeding (Patients 15, 16 and 17).

Diarrhoea is a well known side effect of certain drugs. One such drug is lactulose and indeed all three patients with liver failure who were receiving lactulose, developed diarrhoea. Antibiotic therapy has been frequently associated with diarrhoea[35,56,57,58,59] and this applies particularly to lincomycin and clindamycin[57]. In the present study, no association was noted between diarrhoea and intravenous antibiotic therapy in general. However, treatment with the antibiotic, amikacin, showed significant, albeit marginal, correlation with the occurrence of diarrhoea. Amikacin is a semi-synthetic aminoglycoside and is not a recognised cause of diarrhoea. It is more commonly associated with side effects such as ototoxicity and nephrotoxicity. As amikacin is a relatively new antibiotic there are few publications referring to its use concerning diarrhoea in critically ill patients. Amikacin was, however, given to patients in the study conducted by Gottschlich et al[97]. While these authors did not find an association between any specific antibiotic and the occurrence of diarrhoea their data showed that no less than nine of the twelve patients who were receiving amikacin developed diarrhoea. The possibility that the association found between amikacin and the occurrence of diarrhoea was a spurious one related to abdominal injury was examined. It would appear from the data that while both amikacin and abdominal injury are related to diarrhoea, it is not possible to determine which may be of greater importance.

There has been speculation concerning the possibility that small intestinal bacterial overgrowth may be a significant cause of diarrhoea in critically ill patients[161]. This possibility has not been previously investigated. In the present study, the ^{14}C xylose test of Toskes and King[156] was used as an index of small intestinal bacterial overgrowth. On this basis, only one of the twenty six patients tested had bacterial overgrowth. This particular patient had diarrhoea. In contrast, the metabolism of ^{14}C xylose was significantly lower in the entire group of patients tested when compared with results in a control group. In

addition, patients who had diarrhoea at the time of the ^{14}C xylose test excreted significantly lower amounts of $^{14}CO_2$ than those who did not have diarrhoea. This would strongly suggest that the bacterial flora of the small intestine was significantly depressed in those patients with diarrhoea.

Antibiotics are thought to disturb the normal flora of the gut and this is assumed to lead to small intestinal bacterial overgrowth[56]. Analysis of the results of the ^{14}C xylose tests in the present study suggested that the converse in fact occurred. The possibility of decreased gut motility cannot be excluded as a possible cause of the decreased metabolism of xylose, but this is unlikely as diarrhoea is usually associated with increased gut motility. Excretion of $^{14}CO_2$ was significantly lower in the group of patients who were receiving amikacin at the time of the test when compared to patients who had not received this antibiotic. In addition, patients who had been on amikacin just prior to the test, excreted intermediate amounts of $^{14}CO_2$. The effect of amikacin on the bowel flora is not surprising in view of the broad spectrum activity of this drug against organisms such as Pseudomonas, Escherichia coli, Klebsiella sp, Salmonella and Staphylococcus aureus. Our results also suggest that the bacterial population in the small bowel approaches normality when the amikacin therapy is discontinued. The data in the present study have shown a correlation between the incidence of diarrhoea and treatment with amikacin. In addition, decreased metabolism of ^{14}C xylose, which is indicative of a decreased bacterial population, also correlated with both diarrhoea and amikacin therapy. This suggests that the diarrhoea may be related to the alteration in the bacterial flora produced by this antibiotic. The mechanisms whereby reduced bacterial flora in the small intestine could cause diarrhoea have not been defined. Silk et al have ,however, speculated that the combination of enteral feeding and antibiotic therapy might predispose to diarrhoea[162]. The proposed rationale is based on the role of short chain fatty acids (SCFA) in colonic absorption. SCFA's are known to be powerful stimulants of colonic water and electrolyte absorption. These fatty acids are normally produced in the colon as a result of the metabolism by bacteria of unabsorbed carbohydrate and fibre. Certain antibiotics have been shown to inhibit SCFA production (unpublished observations of Silk et al). It is therefore speculated that the combination of reduced colonic carbohydrate associated with the low fibre content of enteral feeds, and the inhibition of bacterial fermentation by antibiotics, may cause

decreased production of SCFA. This in turn may affect colonic absorption of water and electrolytes and possibly cause diarrhoea.

The prophylactic use of anti-ulcer drugs in the treatment of stress ulceration in critically ill patients is now commonplace. The H_2 receptor antagonists increase the pH of the gastric contents by reducing acid output. The resultant increase in pH may cause bacterial overgrowth and diarrhoea[70]. Indeed, treatment with the H_2 receptor antagonist, cimetidine, has been associated with diarrhoea[31,67]. The anti-ulcer agent , sucralfate, acts by coating the gastric mucosa rather than by affecting acid output. Previous studies have reported that sucralfate neither causes a significant increase in the pH nor promotes the growth of bacteria in gastric juice[68]. In the present study it has been shown that sucralfate was not positively associated with the occurrence of diarrhoea. In addition, results of the ^{14}C xylose test showed that sucralfate had no significant effect on the bacterial flora of the small intestine.

The present study does not allow any conclusions to be drawn on the possible effect of H_2 receptor antagonist therapy on small intestinal bacterial flora.

Our findings regarding hypoalbuminaemia as a cause of diarrhoea, are contrary to those of Brinson and Kolts[49] and Cobb et al[103]. We could find no association between diarrhoea and a serum albumin of less than 26 g/l. This may have a bearing on the type of feeds used in this study as more recent studies have suggested that the diarrhoea associated with hypoalbuminaemia may be induced by the elemental nature of the feed[163]. Use of diets with higher concentrations of peptides has been shown to eliminate the diarrhoea associated with a low serum albumin[164].

The methods used for assessment of nutritional status in the present study were not ideal. However, as no good markers exist at present for the measurement of nutritional status in critically ill patients, it is extremely difficult to assess the status of such patients accurately. The traditional tests such as measurement of serum levels of albumin and transferrin, delayed cutaneous hypersensitivity and even anthropometric measurements such as weight, triceps skinfold thickness and mid upper muscle circumference, are of limited use in the critical care situation as most of these parameters are influenced by changing

metabolic status and fluid compartments[164]. Bearing this in mind, measurement of triceps skinfold thickness and muscle circumference does give an indication of fat and muscle stores and these parameters were therefore used in this study.

According to our criteria, none of the patients studied was severely malnourished. Nutritional status was similar in the two groups and the majority of patients were within the normal ranges for both fat and muscle stores. This is to be expected as most of the patients admitted to intensive care are victims of trauma or sudden severe illness and their nutritional status is therefore usually good. However, the importance of providing adequate nutritional support cannot be over-emphasised as protein loss must be minimised. It is not ideal to provide nutritional support without measuring the patient's nutritional requirements and calculating the amount and type of feed which will meet these requirements. However, the scope of this study is such that it was not possible to examine the full nutritional adequacy of the feeds.

The presence of mild to moderate diarrhoea did not significantly affect the length of time spent in intensive care or the mortality rate. It is therefore perhaps more advantageous to the patient to have mild diarrhoea for 2 or 3 days than to be deprived of nutritional support.

It is extremely difficult to predict whether or not a particular patient will develop diarrhoea. Our results indicate that females are more prone than males to developing diarrhoea. The reason for this is not known. Patients who have experienced severe abdominal injury might be predisposed to diarrhoea. Gastrointestinal liver disease, pancreatic insufficiency and medication cannot be excluded as possible factors in the aetiology of diarrhoea in critically ill patients.

It is important that when diarrhoea does occur, all the possible related factors must be carefully analysed. The data presented have shown that disease, abdominal injury and medication may be associated with the occurrence of diarrhoea. A particularly important finding was that suppression of the intestinal bacterial flora rather than proliferation was associated with diarrhoea and that such bacterial suppression could be attributed to amikacin therapy. In contrast, no association could be demonstrated between diarrhoea and enteral feeding

with either home-made or commercially available feeds. This finding may be due to the selection of feeds and the carefully controlled conditions of administration. Since enteral feeding has been shown to accelerate wound healing, restore cell- mediated immunity and improve nitrogen balance[15], the correct and careful application of this nutritional support technique should prove of considerable benefit in the care of critically ill patients.

CHAPTER 6

CONCLUSION

The study emphasises the multifactorial origin of diarrhoea in critically ill patients. An important conclusion is that no particular factor relating to the composition of the enteral tube feeds was associated with the development of diarrhoea. In addition, the implementation of enteral feeding did not worsen the diarrhoea in patients who had had diarrhoea previously. On the contrary, in the majority of these patients, the diarrhoea improved soon after enteral feeding was started.

The results suggest that the common policy of stopping enteral feeding when patients develop diarrhoea in intensive care be deferred, if possible, while other reasons for the diarrhoea are investigated. The best approach would be to continue enteral feeding unless the diarrhoea becomes unmanageable. Should this occur, enteral feeding may be temporarily stopped and intravenous feeding commenced. Enteral feeding should be re-introduced as soon as possible with careful monitoring of tolerance.

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APPENDIX 1

Pt.No	ICU	Age (yrs)	Race	Sex	Lngth B.R (days)	Diarr bef.	Diarr. aft.	Days feeding	Amik.	Sucral.	Abd.t	Outcome
1*	Surg	70	W	M	4	+mild	-	10	Y	Y	Y	Imp
2	Surg	54	W	M	3	+mild	-	3	Y	N	N	Imp
3*	Resp	18	B	F	10	+mod	+	10	Y	N	N	Imp
4	Surg	50	C	M	3	+mild	+	3	N	Y	Y	Died
5*	Surg	82	W	F	4	+mild	-	4	Y	N	Y	Died
6*	Surg	20	B	M	10	+mod	-	4	Y	N	Y	Imp
7*	Surg	71	W	M	7	+mod	-	12	Y	Y	Y	Imp
8*	Surg	46	W	F	4	+mod	-	3	Y	N	Y	Same
9*	Surg	67	C	F	5	+mod	+	5	Y	N	Y	Same
10*	Surg	32	B	F	4	+mild	+	21	N	Y	N	Same
11*	Surg	26	W	M	6	-	+severe	10	Y	Y	Y	Same
12*	Surg	33	B	F	7	-	+mod	6	Y	Y	Y	Imp
13	Surg	49	C	F	4	-	+mild	3	N	Y	Y	Worse
14*	Surg	47	C	M	5	-	+mild	3	Y	N	Y	Imp
15	Resp	60	W	M	2	-	+mild	4	N	Y	N	Died
16*	Surg	24	C	M	2	-	+mild	3	N	Y	Y	Imp
17	Resp	64	C	M	2	-	+mild	5	Y	N	N	Same
18*	Surg	52	C	F	2	-	+mod	6	Y	Y	Y	Same
19*	Surg	45	W	M	2	-	+mod	3	Y	Y	Y	Imp
20*	Surg	67	C	F		-	+mild	10	N	Y	Y	Died
21*	Surg	75	C	M		-	-	3	Y	Y	Y	Same
22	Resp	40	W	M	2	-	-	4	N	N	N	Died
23	Resp	64	W	M	2	-	-	7	N	N	N	Imp
24	Resp	46	C	M	2	-	-	4	N	Y	N	Died
25	Surg	67	W	M	4	-	-	3	N	Y	Y	Same
26	Resp	38	C	F	8	-	-	5	N	N	N	Imp
27	Surg	48	B	M	2	-	-	3	N	Y	N	Imp
28	Resp	50	C	F	4	-	-	3	N	N	N	Imp
29	Surg	33	B	M	3	-	-	3	N	N	N	Imp
30	Surg	60	W	M	2	-	-	4	N	N	Y	Died
31	Resp	47	W	M	2	-	-	35	N	N	N	Same
32	Resp	25	B	M	2	-	-	4	N	N	N	Same
33*	Resp	60	B	M	2	-	-	5	N	N	N	Imp

34*	Resp	55	B	M	4	-	-	9	N	N	Y	Imp
35*	Surg	45	W	M	2	-	-	5	N	N	N	Imp
36*	Resp	28	C	F	2	-	-	56	N	N	N	Same
37*	Resp	27	C	F	7	-	-	5	N	N	Y	Imp
38	Surg	84	W	M	3	-	-	21	Y	N	Y	Imp
39*	Resp	28	C	M	4	-	-	7	Y	N	N	Imp
40*	Surg	53	B	M	5	-	-	4	N	N	N	Imp
41*	Resp	23	C	M	4	-	-	3	Y	N	Y	Imp
42	Surg	30	C	F	2	-	-	3	Y	N	N	Imp
43*	Surg	25	C	M	4	-	-	3	Y	Y	Y	Imp
44	Surg	73	W	M	4	-	-	28	Y	Y	Y	Same
45	Surg	29	C	M	3	-	-	12	Y	Y	N	Imp
46	Surg	30	B	M	2	-	-	42	Y	Y	Y	Imp
47*	Surg	58	B	M	2	-	-	21	N	N	N	Imp
48*	Surg	65	W	M	4	-	-	14	Y	Y	Y	Imp

Pt = patient, * = bacterial overgrowth test done, ICU = intensive care unit, Lngth B R = length of bowel rest, Diarr Bef = diarrhoea before feeding, Diarr Aft = diarrhoea after feeding, Days feeding = days on enteral feeding, M = male, F = female, W = white, C = coloured, B = black, Surg = surgical intensive care, Resp = respiratory intensive care, amik = amikacin therapy, sucral = sucralfate therapy, abd. t = abdominal trauma, y = YES, N = NO, mod = moderate

APPENDIX 2

DIAGNOSES AND CLINICAL CONDITION OF THE PATIENTS.

PATIENT 1

Leaking abdominal aortic aneurysm, duodenal ulcer. Previous Ca prostrate (Right bilateral orchidectomy) and Ca ascending colon (Right hemi-colectomy). Patient admitted to intensive care after going into respiratory failure. Resistant Staphylococcus cultured from sputum.

Medication:

Clindomycin (600mg i.v, 8hrly), Amikacin (500mg i.v, bd), Pen G (5mU i.v, 6hrly), Flagyl (500mg i.v, 8hrly), Sucralfate (1g orally, 6hrly)

PATIENT 2

Non-insulin dependant diabetes mellitus. Previous infarct, amputation of right toe. Now presented with infection and gas gangrene in foot and leg. Also septicaemic, bedridden and confused.

Medication:

Clindomycin (600mg i.v, 6hrly), Metronidazole (500mg i.v, 8hrly), Amikacin (250mg i.v, 12hrly), Actrapid (50u i.v).

PATIENT 3

Bronchiectasis, pneumonia, respiratory failure. Previous tuberculosis and 5 days post partum on admission. Septicaemic.

Medication:

Ampicillin (1g i.v, 6hrly), Amikacin (350mg i.v. bd), Flagyl (500mg i.v, 8hrly), Ventolin 1:4, 4hrly), Kloref (2 orally, bd), Prednisone (30mg orally, daily), Pipricillin (2g i.v, 6hrly), Aminophyllin (1g/200ml i.v, 9ml/hr), Pyridoxine (50mg orally, daily), INH (300mg orally, daily), Metronidazole (500mg i.v, 6hrly).

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PATIENT 2

Non-insulin dependant diabetes mellitus. Previous infarct, amputation of right toe. Now presented with infection and gas gangrene in foot and leg. Also septicaemic, bedridden and confused.

Medication:

Clindamycin (600mg i.v, 6hrly), Metronidazole (500mg i.v, 8hrly), Amikacin (250mg i.v, 12hrly), Actrapid (50u i.v).

PATIENT 3

Bronchiectasis, pneumonia, respiratory failure. Previous tuberculosis and 5 days post partum on admission. Septicaemic.

Medication:

Ampicillin (1g i.v, 6hrly), Amikacin (350mg i.v. bd), Flagyl (500mg i.v, 8hrly), Ventolin 1:4, 4hrly), Kloref (2 orally, bd), Prednisone (30mg orally, daily), Pipricillin (2g i.v, 6hrly), Aminophyllin (1g/200ml i.v, 9ml/hr), Pyridoxine (50mg orally, daily), INH (300mg orally, daily), Metronidazole (500mg i.v, 6hrly).

PATIENT 4

Bleeding oesophageal varices, ethanolic cirrhosis, hepatic encephalopathy. Ascites present. Patient pyrexial and in multiple organ failure 6 days after admission. Active treatment withdrawn.

Medication:

Lactulose (20ml orally, 8hrly), Aldactone (50mg orally, 12 hrly), Sucralfate (1g orally QID), Ampicillin (500mg i.v, 6hrly), Cefotaxime (1g i.v, 6hrly).

PATIENT 5

Ruptured abdominal aortic aneurysm. At operation, rupture into left colon, mesentery and sigmoid mesocolon. Patient developed collapse of left lung. Also hypertensive.

Medication:

Ventolin (1:4 , 4hrly), Penicillin (2mU i.v, 6hrly), Amikacin (500mg i.v, prn), Morphine (5mg i.v, prn), Diazepam (5mg i.v, prn).

PATIENT 6

Lacerated stomach due to stab wounds, hole in diaphragm, soiled abdomen. Emergency laparotomy. Respiratory failure, cardiac failure, right cerebral infarct. Hypertensive and in septic shock.

Medication:

Amikacin (500mg i.v, daily), Pen G (2 megaU i.v, 6hrly), Flagyl (1g i.v 12 hrly), Cloxacillin (2g i.v, 6hrly).

PATIENT 7

Ruptured abdominal aortic aneurysm. Retroperitoneal bleeder found and tied off. No previous medical problems.

Medication:

Pen G (2 megaU i.v, 6hrly), Amikacin (500mg i.v, 6hrly), Epanutin (300mg i.v, bd), Digoxin (o.25g i.v, daily), Sucralfate (1g orally, 8hrly), Nystatin (1ml orally, 6hrly).

PATIENT 8

Bleeding oesophageal varices, chronic liver disease, malaena stools and vomiting, clinically jaundiced.

Medication:

Neomycin (1g orally, 6hrly), Lactulose (20ml orally, 8hrly), Ranitidine (50mg i.v, 8hrly), PenG (2megaU i.v, 6hrly), Amikacin (500mg i.v, 12hrly), Flagyl (500mg i.v, 8hrly), Aldactone (200mg i.v, 12hrly), Clindomycin (600mg i.v, 8hrly), Lasix (10mg i.v, 6hrly).

PATIENT 9

Respiratory arrest, cardiac arrest, bleeding gastric ulcer. Patient underwent Bilroth 1 gastrectomy.

Medication:

PenG (5 megaU i.v, 6hrly), Morphine (10mg i.v, 4hrly), Amikacin (500mg i.v, bd), TNT (50mg/200ml i.v, 30dpm), Cloxacillin (1g i.v, 6hrly).

PATIENT 10

Multiple fractures and head injury following motor accident.

Medication:

Penicillin (5megaU i.v, 6hrly), Sucralfate (1g orally, 6hrly), Cloxacillin (2g i.v, 6hrly).

PATIENT 11

Wall fell on patient's chest. Left pneumothorax, left flank haematoma, left hemispherical infarct, liver damage, bowel ischaemia.

Medication:

Sucralfate (1g orally, 6hrly), Cloxacillin (2g i.v, 6hrly), Amikacin (500mg i.v, 12hrly), Morphine (50mg i.v, 2 hrly), Clindamycin (600mg i.v, 8hrly), Cefotaxime (1g i.v, 6hrly), Lasix 20mg i.v, 6hrly).

PATIENT 12

Acute haemorrhagic pancreatitis. Abortion at 24 weeks two weeks prior to admission.

Medication:

Sucralfate (1g orally, 6hrly), Valium (5mg i.v, 4hrly), Amikacin (500mg i.v, 12hrly), Flagyl (500mg i.v, 8hrly), PenG (2 megaU i.v, 6hrly), Actrapid (sliding scale).

PATIENT 13

Patient involved in motor accident. Broken humerus, compound fracture of tibula/fibula, lacerated spleen (splenectomy), contused small bowel, large incisional hernia. Jaundiced. Developed abdominal abscess in intensive care just before going onto trial.

Medication:

PenG (5 megaU i.v, 6hrly), Morphine (2mg i.v, prn), Sucralfate (1g orally, 6hrly).

Patient 14

Liver failure, bleeding oesophageal varices, portal hypertension, hepatic encephalopathy, ascites and cirrhosis.

Medication:

Lactulose (30ml orally, 8hrly), Neomycin (1g orally, 8hrly), Penicillin (2 megaU i.v, 6hrly), Amikacin (500mg i.v, bd), Aldactone (50mg i.v, 6hrly).

PATIENT 15

Myelodysplastic syndrome. Respiratory failure secondary to klebsiella pneumonia.

Medication:

Flagyl (400mg orally, 8hrly), Mycostatin (4ml orally 4 hrly), Digoxin (0.25mg orally, 6hrly), Cefotaxime (1g i.v, 6hrly), Sucralfate (2g orally, 12hrly).

PATIENT 16

Post MVA. Head injury, generalized brain swelling. Also episode of dark vomitus, query acute gastritis.

Medication:

Bactrim (1amp i.v, bd), Decadron (8mg i.v, 8hrly), Valium (5mg i.v, 6hrly), Morphine (5mg i.v, 2hrly), Etomine (80mg i.v, 6hrly), Sucralfate (1g orally, 6hrly).

PATIENT 17

Known COAD. Steroid induced bronchospasms caused respiratory arrest and chest infection.

Medication:

Hydrocortisone (200mg i.v, 4hrly), Aminophyllin (250mg i.v, 6hrly), Amikacin (400mg i.v, bd), Penicillin (2megaU i.v, 6hrly), Potassium chloride (10ml orally, 6hrly), Ventolin (10mg/200ml i.v, daily), Monotard (5units bd).

PATIENT 18

Post MVA. Multiple trauma. Ruptured left hemidiaphragm, small retroperitoneal haematoma, lateral dislocation of the knee, respiratory distress, hypertensive.

Medication:

Morphine (5mg i.v, prn), Diazapam (5mg i.v, prn), Sucralfate (1g orally, 6hrly), Penicillin (2macroU i.v, 6hrly), Amikacin (400mg i.v, bd).

PATIENT 19

Post MVA. Large left haemothorax, lung contusions, acute abdomen, haematuria, ruptured diaphragm, shattered spleen and some bowel in chest. Patient had two laparotomies and developed respiratory failure post-op.

Medication:

Morphine (5g i.v, 2hrly), Valium (10g i.v, prn), Sucralfate (2g orally, 6hrly), Ventolin nebs (1:4, prn), Cloxacillin (2g i.v, 6hrly), Epanutin (200mg i.v, 8hrly), Amikacin (500mg i.v, 12hrly), Aminophyllin (400mg i.v, 6hrly).

PATIENT 20

Admitted one month previously. Gastric ulcer found. Developed respiratory distress in ward and G.I rebleed. Gastrectomy done. Patient to I.C.U. Became septicaemic, hyperglycaemic and developed respiratory distress. Patient also develped prolapsed pile and became jaundiced. When put onto trial patient was much improved.

Medication:

Sucralfate (1g orally, 6hrly), Flagyl (500mg i.v, 8hrly), Ventolin (1:4, 4hrly), Cefotaxime (1g i.v, 6hrly), Amphotericin B (10mg i.v, 6hrly).

PATIENT 21

Abdominal aortic aneurysm. Adult respiratory distress syndrome. Patient sent to intensive care following prolonged procedure for repair of ruptured abdominal aortic aneurysm. Problems of hyperkalaemia and oliguria. Also bleeding from colic artery. Mild jaundice. Patient entered into trial 10 days post-op.

Medication:

Amikacin (250mg i.v, bd), Flagyl (500mg i.v, 8hrly), PenG (2macroU i.v, 6hrly), Sucralfate (1g orally, 6hrly), Vancomycin (1g i.v, bd).

PATIENT 22

Hodgkins lymphoma, progressive muscle weakness, respiratory failure, radiation pneumonitis. Patient received total body irradiation and given double dose by mistake.

Medication:

Prednisone (20mg oraly, daily), Erythromycin (500mg orally, 6hrly), Ipradol (1:4)

PATIENT 23

Chronic obstructive airways disease, iron deficiency anaemia, recto-sigmoid polyp, chest infection. Patient admitted with swollen ankles and tight chest. Admitted to medical ward. Then developed severe respiratory distress and had to be intubated and ventilated.

Medication:

Bactrim (10mg i.v, bd), Ventolin (10mg i.v, daily), Hydrocortisone (200mg i.v, 4hrly), Aminophyllin (250mg i.v, 6hrly), Iron sulphate (200mg orally, tds), Ranitidine (50mg i.v, tds), Valium (10mg i.v, prn), Fentonyl (1amp i.v, prn), Moduretic (2 orally, daily).

PATIENT 24

Patient admitted to trauma unit due to severe burns (16%) to face, scalp, chest and hand. Also large amounts of soot in nose and pharynx. Upper airways obstruction.

Medication:

Sucralfate (1g orally, 6hrly), Penicillin (2macroUi.v, 6hrly), Ventolin (1:4, 4hrly), Morphine (2mg i.v, prn), Valium (5 - 10mg i.v, prn).

PATIENT 25

Emergency surgery for ruptured abdominal aortic aneurysm. Known hypertensive. Patient became jaundiced and septicaemic and developed poor urine output. Patients conditioned had improved by the time he was started on this trial..

Medication:

Cefotaxime (1g i.v, 6hrly), Sucralfate (1g orally, 6hrly).

PATIENT 26

Patient was a known steroid dependant asthmatic. Admitted with bronchospasm which did not respond to pump. Severe asthma attack due to right upper lobe lung infection.

Mediation:

Prednisone (60mg orally, daily), Ranitidine (150mg orally, bd), Amoxyl (500mg orally, tds), Clindamycin (600mg i.v, 6hrly), Vancomycin (1g orally, 12 hrly), Salbutamol (10mg/1000ml, daily), Euphyllin retard (2,5 tabs bd).

PATIENT 27

Patient referred from general medical ward with respiratory failure. Background history of PTB, COAD.

Medication:

Lasix (40mg i.v, bd), Hydrocortisone (100mg i.v, 4hrly), Spironolactone (5g orally, daily), PenG (2G=g i.v, 6hrly), Ipradol (1:4, 6hrly), INH (500mg orally, daily), Sucralfate (1g orally, 6hrly), Ampicillin (500mg i.v, 6hrly).

PATIENT 28

Patient was known to suffer from asthma and COAD. Admitted due to increasing shortness of breath and green sputum production. Condition deteriorated with cyanosis, wheeze. Patient also became pyrexial.

Medication

Aminophyllin (400mg i.v, 12hrly), Ventolin (1:4 inhaled, 4hrly), Atropine (1:4 inhaled, 4hrly), Hydrocortisone (200mg i.v, 4hrly), Ampicillin (500mg i.v, 6hrly), Ranitidine (50mg i.v, 8hrly).

PATIENT 29

Patient assaulted with a lead pipe. Fractured skull and mandible, chest complications, small pneumothorax.

Medication:

Morphine (20mg/200ml i.v, 5 drops/minute), PenG (2macroU i.v, 6hrly), Flagyl (500mg i.v, 8hrly).

PATIENT 30

Patient admitted for intensive care post surgery after removal of a septic bifemoral graft repair. Patient in septic shock, respiratory failure.

Medication:

Flagyl (500mg i.v, 8hrly), Penicillin (5macroU i.v, 6hrly), Valium (5g i.v, prn), Cloxacillin (1g i.v, 6hrly), Morphine (5mg i.v, prn), Gentamycin (60mg i.v, 8hrly).

PATIENT 31

Guillain-Barre syndrome, chronic schizophrenia. Patient developed weakness in hands and feet. Admitted with polyradiopathy.

Medication:

Stelazine (2 orally, bd), Benzhexol (2mg orally, bd), Amoxyl (500mg orally, tds).

PATIENT 32

Known asthmatic. Admitted with severe respiratory distress due to bronchospasm. Also bradycardia, chest infection. Patient unconscious at the time of the trial.

Medication:

Flagyl (500mg i.v, 8hrly), Epanutin (100mg i.v, 8hrly), Euphyllin retard (2 tabs orally, 12hrly), Prednisone (40mg orally, daily).

PATIENT 33

Post MVA. COAD, broken ribs, pulmonary contusion, complete collapse of left lung.

Medication:

Aminophyllin (250mg i.v, 6hrly), Ventolin (1:4, 4hrly), Ampicillin (1g i.v, 6hrly), Morphine (5mg i.v, prn).

PATIENT 34

Post MVA. Multiple trauma. Flail chest, contused lung, respiratory distress, lacerated scalp, haematuria, possible intra-abdominal bleed.

Medication:

Penicillin (2.5 macroU i.v, 6hrly), Ipradol (1:4, 12hrly), Panadeine (2 orally, 6hrly).

PATIENT 35

Patient involved in motorcycle accident. Head injury, unconscious. Broken ribs and right femur.

Medication:

Penicillin (5macroU i.v, 6hrly), Valium (5mg i.v, 6hrly).

PATIENT 36

Patient admitted to intensive care due to respiratory failure. Previously diagnosed tuberculosis. Patient could not keep T.B medicine down. Fainted and hit the back of her head. Left eye vision and limb movement began to deteriorate. Tentative diagnosis of Devick's syndrome.

Medication:

Medrol (1g i.v, daily), Rifampicin (450mg orally, daily), PZA (1g orally, daily), Pyridoxine (25mg orally, daily).

PATIENT 37

MVA pedestrian. Deaf mute. Multiple trauma, right pneumothorax, laceration of liver, contusions of small bowel. Multiple broken bones.

Medication:

PenG (5macroU i.v, 6hrly), Cloxacillin (2g i.v, 6hrly), Ventolin (1:4, 4hrly), Valium (5mg i.v, prn), Fetanyl (100mg i.v, daily).

PATIENT 38

Small bowel obstruction relieved by laparotomy 2 weeks prior to being admitted to intensive care. Patient developed streptococcal pneumonia, became pyrexial. Level of consciousness deteriorated.

Medication:

Digoxin (0.25mg i.v, daily), Actrapid (sliding scale), PenG (2megaU i.v, 6hrly), Clindamycin (600g i.v, 8hrly), Isordil (10mg orally, 6hrly), Phenytoin (100g i.v, tds), Cloxacillin (2g i.v, 6hrly), Amikacin (500mg i.v, bd).

PATIENT 39

Kartagener's syndrome, bronchiectasis, septicaemia. Patient required intubation and ventilation.

Medication:

Penicillin (2macrou i.v, 6hrly), Amikacin (400mg i.v, 12hrly), Ventolin (1:4. 4hrly), Flagyl (500mg i.v, 8hrly), Pipericillin (1g i.v, 6hrly).

PATIENT 40

Abscess on left buttock. Previous operations for abcesses and anorectal fistulae. Pyrexial, septicaemic after operation to remove abcess.

Medication:

Penicillin (2macroU i.v, 6hrly), Flagyl (500mg i.v, 8hrly), Ventolin (1:4, 6hrly), Valium (10mg i.v, 6hrly), Morphine (5mg i.v, 6hrly), PenG (5macroU i.v, 6hry), Aminophyllin (250mg/200ml i.v, 6hrly).

PATIENT 41

Multiple stabs to chest, bilateral pneumothorax, right surgical emphysema, wheezing.

Medication:

Ventolin (15mg i.m, 6hrly), Aterax (50mg i.m, 6hrly), Ampicillin (2g i.v, 6hrly), Amikacin (400g i.v, 12hrly).

PATIENT 42

Post MVA. ARDS, fat embolus, broken pelvis, broken femur, ruptured bladder. Admitted to ICU because of developement of fat embolus, ARDS.

Medication:

Morphine (10mg i.m, 6hrly), Penicillin (5macroU, 6hrly), Amikacin (500mg i.v, bd), Flagyl (1g orally, 8hrly).

PATIENT 43

Post MVA. Multiple trauma, scalp laceration, broken pelvis, retroperitoneal haematoma.

Medication:

PenG (2macroU, i.v, 6hrly), Sucralfate (1g orally, 6hrly), Amikacin (500mg i.v, 12hrly), Ampicillin (1g i.v, 6hrly).

PATIENT 44

Hepatic carcinoma. Previous prostatectomy. Admitted after respiratory arrest, bleeding in abdomen. Bleeding liver tumour found on laparotomy.

Medication:

Sucralfate (1g orally, 6hrly), Flagyl (500mg i.v, 8hrly), PenG (2macroU i.v, 6hrly), Amikacin (500g i.v, 12hrly).

PATIENT 45

Stab to left side of neck. Major venous injury, tracheal injury. Hypoxia, wound sepsis.

Medication:

Amikacin (500mg i.v, 12hrly), Cloxacillin (2g i.v, 6hrly), Flagyl (500mg i.v, 8hrly), Sucralfate (1g orally, 8hrly).

PATIENT 46

Post MVA. Head injury, blunt injury to chest, unconscious, periphrenic haematoma.

Medication:

Morphine (50mg/200ml i.v), Sucralfate (1g orally, 6hrly), Amikacin (500g i.v, 12hrly), PenG (2megaU i.v, 6hrly).

PATIENT 47

Multiple injuries due to heavy fall. Retroperitoneal haematoma, both legs broken, possible head injury.

Medication:

Cloxacillin (1g i.v, 6hrly), Morphine (10mg i.v, prn), Valium (10mg i.v, 2hrly).

PATIENT 48

Ulcerative colitis since 1964. Total colectomy and ileostomy done in 1986. Admitted to intensive care with bowel distension following revision of ileostomy. 30cm of ischaemic bowel resected, multiple adhesions.

Medication:

Sucralfate (1g orally, 6hrly), Amikacin (400mg i.v, bd), Ventolin (0.25mg i.v, daily), Thioridazine (25mg orally, daily).