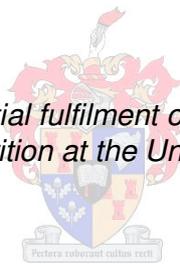


**The effect of a low volume pharmaconutrition supplement with antioxidants and glutamine (Intestamine®) administration to critically ill patients on the prevalence of infection, ventilation requirements and duration of intensive care unit stay: A Pilot Study**

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*Thesis presented in partial fulfilment of the requirements for the degree Master of Nutrition at the University of Stellenbosch*



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December 2010

## **DECLARATION**

By submitting this thesis electronically, I Hester Susanna Van Niekerk, declare that the entirety of the work contained therein is my own original work, that I am the owner of the copyright thereof, (unless to the extent explicitly otherwise stated) and that I have not previously submitted it for obtaining any qualification in its entirety or in part thereof.

Signature: HS van Niekerk

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## **ABSTRACT**

### **Introduction**

Complications of severe infection or acute trauma include a cascade of immunological dysfunctions known as SIRS (Systemic Inflammatory Response Syndrome), that affect response to treatment, prolonging and complicating the course of illness and jeopardizing clinical outcome. Timing and the nature of nutritional support in the Intensive Care Unit (ICU) setting may influence this process. Against this background, and despite some trials demonstrating beneficial clinical outcomes for the use of immune-modulating diets (IMD), the findings of the US summit on immune-enhancing enteral therapy concluded that the currently available enteral immune-enhancing formulas are “first-generation products” which may not be appropriate in patients with SIRS or severe sepsis. This highlights a need for alternative nutritional products that target the specific needs of this patient population. As such, Intestamin® is designed for use in severely stressed patients as an immune-modulating enteral feed supplement which aims to improve maintenance of gut barrier integrity and immune response.

### **Aim**

The aim of this pilot study was to investigate the effect of Intestamin® administration to critically ill patients, and in particular, to determine if administration would impact on nosocomial infections, ventilation days and the length of stay in the ICU.

### **Methods**

The study design was an open label, retrospective case control, analytical study, of patients admitted to the ICU in The Bay Hospital, Richards Bay, between January 2002 and November 2003, who received Intestamin®. Patients were selected for the study from post-surgery and post-trauma patients at high risk of sepsis and SIRS, and critically ill patients with manifested SIRS or severe sepsis. Development of respiratory and urinary sepsis was used as surrogate markers for progression to severe sepsis and SIRS. Additionally, duration of ventilation

and ICU stay were considered representative of the response to treatment and degree of clinical complications.

### **Results**

The findings of the study demonstrated a significant difference in the rates of respiratory infection( $p=0.05$ ), positive sputum and tracheal aspirate cultures( $p=0.03$ ) and urinary catheter tip cultures( $p=0.04$ ). with statistically lower rates in the intervention group compared to the control group. There were no significant differences in the rates of urinary tract infection, septicaemia or in combined sepsis rates between the two groups. There were statistically significant higher rates of positive pus cell counts in the sputum( $p=0.003$ ) and urine( $p=0.01$ ) in the intervention group, compared to the control group. No corresponding reduction in ventilation days or ICU stay was observed.

### **Conclusion**

In this patient population, early enteral nutrition with specially formulated IMD, (Intestamin®), did result in a significant reduction in respiratory infections, but not in other types of sepsis, ICU or ventilator days in critically ill ICU patients. This positive finding in some, but not all endpoints collected, may reflect confounding factors in the small patient population or the choice of clinical endpoints, rather than a genuine limitation in the benefit. IMD remains a tantalizing and scientifically plausible intervention in this patient population, with larger clinical trials necessary to confirm outcomes. The study supports the safe use of Intestamin by the nasojejunal route in this patient population.

## **OPSOMMING**

### **Inleiding**

Komplikasies van erge infeksie of akute trauma sluit 'n kaskade van immunologiese disfunksie in, bekend as SIRS (Sistemiese Inflammatoriese Respons Sindroom), wat die respons op behandeling affekteer, die verloop van siekte verleng en kompliseer asook die kliniese uitkoms beïnvloed. Tydsberekening en die aard van die voedingsondersteuning in die Intensiewe Sorg Eenheid (ISE) mag hierdie proses beïnvloed. Teen hierdie agtergrond, en ten spyte van sommige studies wat die voordelige kliniese uitkoms vir die gebruik van immuun-modulerende diete (IMD) toon, het die "US summit" oor immuun-verbeterde enterale terapie tot die gevolgtrekking gekom dat die huidige beskikbare enterale immuun-verbeterde formules, "eerste-generasie" produkte is, wat moontlik nie toepaslik is vir pasiënte met SIRS of erge sepsis nie. Dit beklemtoon 'n behoefte aan alternatiewe voedingsprodukte wat die spesifieke behoeftes van die genoemde pasient populasie teiken. Intestamin® is ontwerp vir gebruik in erge gestresde pasiënte as 'n immuun-modulerende enterale voedingssupplement doelgerig om spysverteringskanaal integriteit te onderhou en immuniteit te verbeter.

### **Doel**

Hierdie loodsstudie se doel was om die effek van Intestamin® toediening aan kritiek siek pasiënte te ondersoek, spesifiek om vas te stel of die toediening impakteer op nosokomiale infeksies, ventilasie dae en dae in ISE.

### **.Metode**

Die studie ontwerp was 'n oop, retrospektiewe, geval kontrole, analitiese studie van pasiënte opgeneem in die ISE van The Bay Hospital, Richardsbaai, tussen Januarie 2002 en November 2003, wat Intestamin® ontvang het. Pasiënte is geselekteer vir die studie uit post-chirurgies en post-trauma pasiënte wat hoë risiko was vir sepsis en SIRS, en kritiek siek pasiënte wat reeds manifesteer het met SIRS of erge sepsis. Ontwikkeling van respiratoriese en urinêre sepsis is gebruik as surrogaat merkers vir die progressie na erge sepsis en SIRS.

Addisioneel is duur van ventilasie en ISE verblyf beskou as verteenwoordigend vir die respons op behandeling en die graad van kliniese komplikasies.

### **Resultate**

Die bevindinge van die studie het betekenisvolle verskille aangedui in die voorkoms van respiratoriese infeksies( $p=0.05$ ), positiewe sputum en trachiale aspiraatkulture( $p=0.03$ ) en urine kateterpunt-kulture( $p=0.04$ ) met statistiese laer voorkoms in die intervensie groep in vergelyking met kontroles. Geen statistiese verskille in die voorkoms van urineweg-infeksies, sepsis of in gekombineerde sepsis voorkoms tussen die twee groepe is gevind nie. Daar was statistiese betekenisvolle hoër voorkoms van etterselle hoeveelhede in die sputum( $p=0.030$ ) en urine( $p=0.01$ ) van die intervensie groep in vergelyking met die kontrole groep. Geen ooreenkomstige vermindering in ventilasie dae of ISE verblyf is opgemerk nie.

### **Gevolgtrekking**

In hierdie pasiënt populasie, het vroeë enterale voeding met spesifieke geformuleerde IMD (Intestamin®), 'n beduidende vermindering in respiratoriese infeksies getoon, maar nie in ander tipes sepsis, ISE of ventilasie dae by kritiek siek pasiënte nie. Hierdie positiewe bevindinge in sommige, maar nie al die versamelde eindpunte nie, reflekteer moontlike bydraende faktore in die klein pasiënt populasie of die keuse van kliniese eindpunte, eerder as 'n ware beperking in die voordele. IMD bly steeds 'n uitdagende en wetenskaplik uitsonderlike intervensie in hierdie pasiënt populasie, wat groter kliniese studies benodig om die uitkoms te bevestig. Die studie ondersteun die veilige gebruik van Intestamin® via die nasojejale roete in kritiek siek pasiënte.

## **DEDICATION**

For my late Dad, I finished this because of your belief in me.

## **ACKNOWLEDGEMENTS**

A special word of thanks to my dear husband who spent hours behind the computer to help me design tables, graphs and find lost documents. Henk, thank you for supporting me and keeping me going. The staff at Netcare The Bay Hospital ICU, thanks for keeping to the study protocol. A special thank you to Dr Gunther Kelling and Dr Pieter van Rooyen for always being available to answer questions when things did not make sense to me. Thanks to Prof Demetre Labadarios (study leader) and Janicke Visser (co-study leader) for their encouragement and patience. The laughter and love of family and friends (Coffee Club) were invaluable and the understanding of colleagues cannot go unmentioned. Last but definitely not least at all, a special thanks to Dr Christine Kelbe, who gave this thesis a “heart”, who spent hours listening to questions and helped with the interpretation of the data, motivated me when times were tough and just kept going despite any hiccoughs. Chris, this paper was like “rolling like a ball” to you in Pilates. There are no words to thank you enough.

## LIST OF ABBREVIATIONS

APACHE	:	Acute Physiological Assessment and Chronic Health Evaluation <sup>1</sup>
ARDS	:	Adult respiratory distress syndrome <sup>1 2</sup>
CRP	:	C-Reactive protein <sup>1 3</sup>
EEN	:	Early enteral nutrition <sup>1 4</sup>
EN	:	Enteral nutrition <sup>1 4</sup>
GALT	:	Gut associated lymphoid tissue <sup>1 5</sup>
GSH	:	Glutathione in the reduced, monomeric form <sup>1 6</sup>
GSSG	:	Glutathione in the oxidized, dimeric form <sup>1 6</sup>
GI	:	Gastrointestinal <sup>1 6</sup>
ICU	:	Intensive care unit <sup>1 7</sup>
IMD	:	Immune-modulating diets <sup>1 4</sup>
LCFA	:	Long chain fatty acids <sup>1 8</sup>
MODS	:	Multiple organ dysfunction syndrome <sup>1 9</sup>
MOF	:	Multiple organ failure <sup>1 9</sup>
OFR	:	Oxygen free radicals <sup>1 10</sup>
SCFA	:	Short chain fatty acid <sup>1 10</sup>
SIRS	:	Systemic inflammatory response syndrome <sup>1 11</sup>
TNF	:	Tumour necrosis factor <sup>1 12</sup>

## LIST OF DEFINITIONS

### **Control group:**

The group of subjects who did not receive the product Intestamin®

### **Ileus:**

An inhibition of the propulsive intestinal motility <sup>13</sup>

### **Intervention group:**

The group of subjects who received the product Intestamin®

### **Multiple organ dysfunction syndrome:**

The term which is applied to acutely ill patients with altered organ functions, who are unable to maintain metabolic homeostasis. <sup>11</sup>

### **Sepsis:**

Defined as the *inflammatory response to infection*, thus representing a subentity of SIRS. Sepsis is SIRS from an infectious insult. <sup>11</sup>

### **SIRS:**

The *systemic inflammatory response* to any severe insult, be it *infectious or noninfectious*. <sup>11</sup>

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## **CHAPTER 1 : INTRODUCTION AND RESEARCH QUESTION**

## INTRODUCTION

The consensus recommendations of the summit on immune-enhancing enteral therapy, highlight a need to develop alternative nutritional products which target the specific needs of the critically ill. Extrapolating on the results for conventional immune enhancing diets in other patient populations, this may constitute an additional strategy to positively influence the course of the metabolic and immunological dysfunction in critically ill patients.<sup>11</sup>

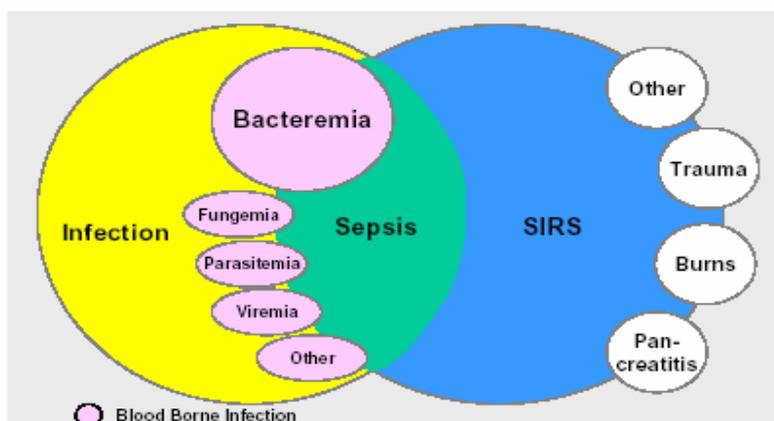
In order to understand the scope for nutritional immunomodulation in these patients, it is necessary to identify the underlying pathophysiological processes which lead to immune dysregulation and SIRS as well as the consequences of this response in the body. These processes will be described, with particular emphasis on those key systems influenced or modified by the nature and timing of the nutritional support provided.

This will be used to highlight the justification for new generation enteral feeds, as represented by Intestamin®, over conventional first generation products and the reason Intestamin® was chosen as a nutritional intervention in this study of outcome of critically ill ICU patients.

### 1.1 THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

**SIRS** is defined as a **systemic inflammatory response** to any severe insult, both **infectious and noninfectious**. These may include conditions such as pancreatitis, ischemia, multiple trauma and tissue injury, hemorrhagic shock or burns. The use of the term SIRS is independent of the triggering insult.<sup>14</sup>

**Sepsis is** defined as the **inflammatory response to infection** and is one cause of SIRS. Sepsis is therefore a risk factor for SIRS.<sup>11</sup> (Figure 1.1)



**Figure 1.1 The relationship between systemic inflammatory response syndrome (SIRS), sepsis, and infection**  
 (Source: Martindale RG, Sawai R 2007<sup>14</sup>)

**Sepsis, severe sepsis, septic shock and SIRS** represent a continuum of clinical and pathophysiological severity which is correlated with increasing organ dysfunction and mortality.<sup>15, 16</sup>

Multiple organ dysfunction syndrome (MODS) is the term which is applied to acutely ill patients with altered organ dysfunction, who are unable to maintain metabolic homeostasis.<sup>11</sup>

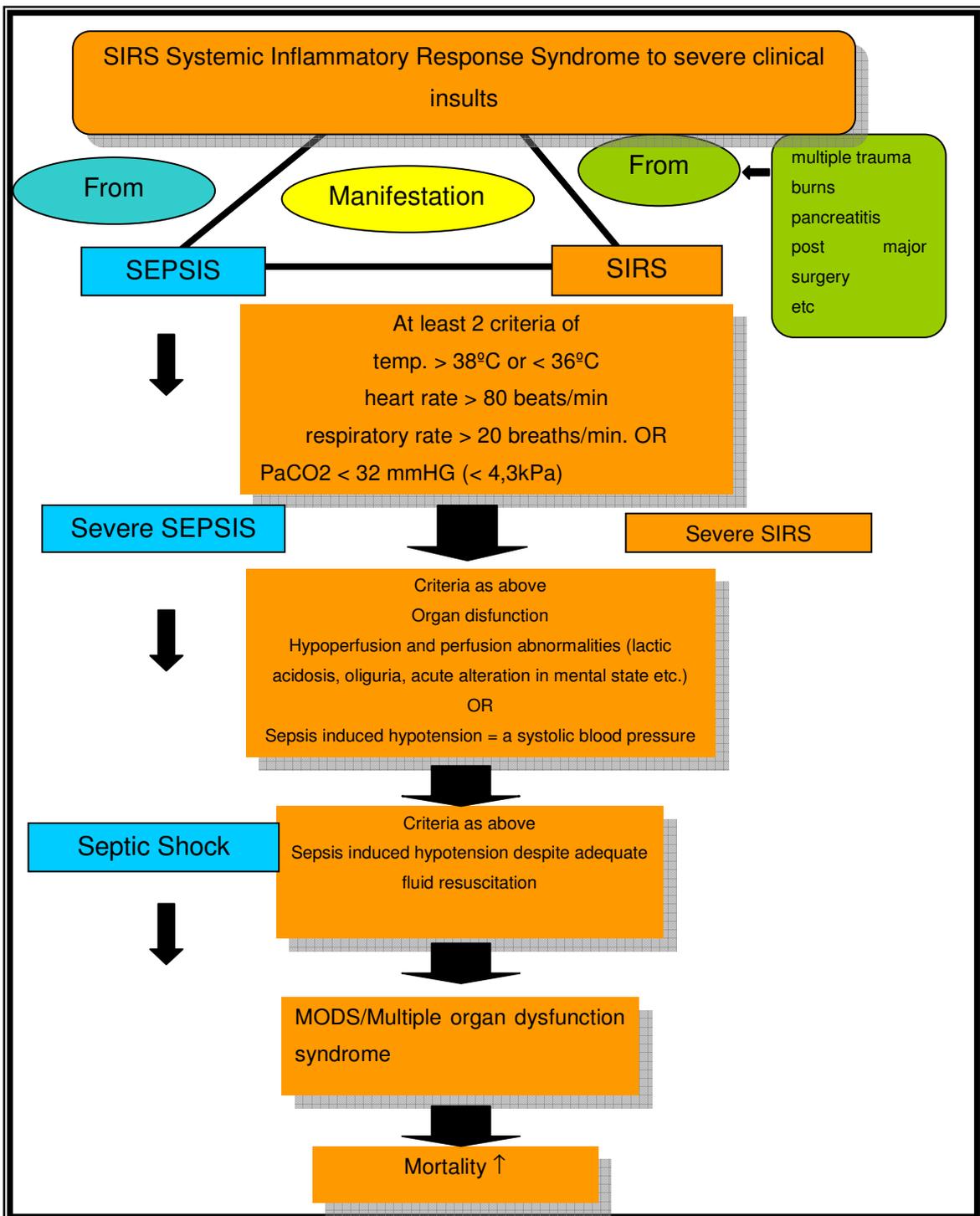
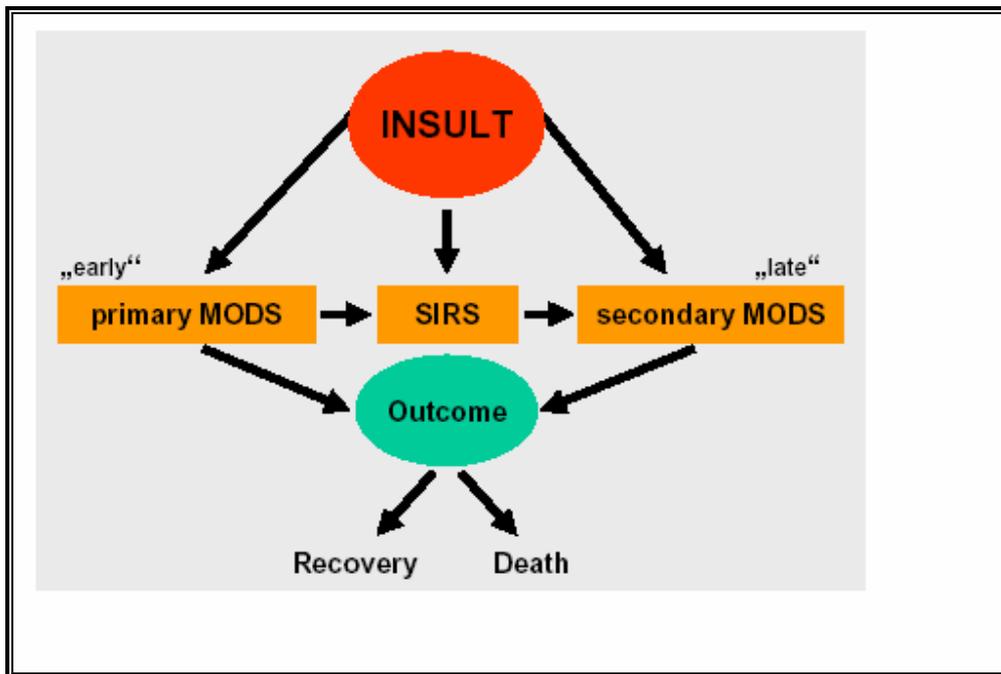


Figure 1.2 Dynamic process from SIRS and SEPSIS to MODS as defined by the 1991 Consensus Conference (Source: Alberti et al. 2002<sup>15</sup> Matot I, Sprung CL 2001<sup>16</sup>)

MODS, analogous to SIRS, represents a continuum of physiological derangements. It describes a dynamic process of increasing pathological severity. MODS is a frequent complication of SIRS and may be considered the more severe end of the spectrum of SIRS and sepsis. It is viewed as a complication of SIRS and sepsis, to be prevented, rather than a disease to be treated. MODS may be described as being either primary or secondary (Figure.1.3).



**Figure 1.3 The different causes and results of primary and secondary multiple organ dysfunction syndrome (MODS)**

**(Source: Brun-Buisson C 2000. <sup>17</sup>)**

Primary MODS results immediately from a primary insult, e.g. pulmonary contusion, whereas secondary MODS results rather later from SIRS or sepsis..<sup>11</sup>

The incidence of SIRS and sepsis is still very high in the ICU setting and correlates with a high mortality. The retrospective study by Brun-Buisson calculated the prevalence of severe sepsis and shock to be 10-15 % of all ICU patients <sup>17</sup> and the recently published prospective cohort study by Alberti et al <sup>15</sup>

documented a similar prevalence, with 25% of all patients who stayed longer than 24 hours in the ICU developing severe sepsis and/or septic shock.

The 28-day mortality rate for severe sepsis is approximately 20-40% and that for septic shock 40-60%. Due to tremendous progress in the initial care of severe trauma patients, early mortality has been reduced over the last years. Late mortality, however, is still high and related to the high incidence of SIRS and MODS. It is evident, therefore, that there is a need for promising new approaches to treat and prevent SIRS, sepsis and its sequelae.<sup>18</sup>

Based on the given scientific rationale, Intestamin® may belong to these new promising approaches.

## **1.2 SIRS METABOLISM AND NUTRITIONAL IMPLICATIONS**

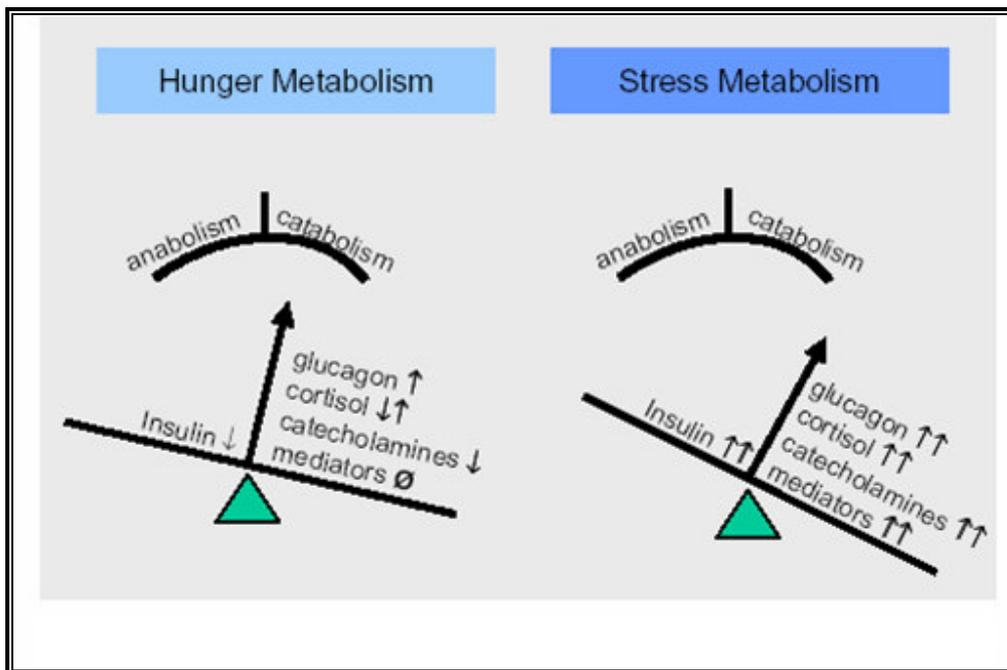
The goal of this chapter is to learn why “too many calories and the wrong combination of caloric substrates can do more harm than good” during SIRS and MODS. The review article by Kim et al<sup>19</sup> is the main source for the following explanation.

Catabolism is the metabolic response to both stress and hunger, usually referred to as hypermetabolism. There is, however, a profound difference in the extent to which substrates may be utilized for stress and for hunger.<sup>19 20</sup>

As both metabolic situations may occur in the critically ill, it is important to know what the differences between stress and hunger metabolism are and also the nutritional consequences of these responses.<sup>19 20</sup>

During hunger, substrate utilization is not impaired. Substrate utilization adapts to nutrient availability. Consequently, increased substrate supply may reverse hunger-induced catabolism. During stress, however, substrate utilization is impaired. Catabolism, that is the increased mobilization of endogenous energy and protein stores, cannot be reversed or stopped but only be reduced by

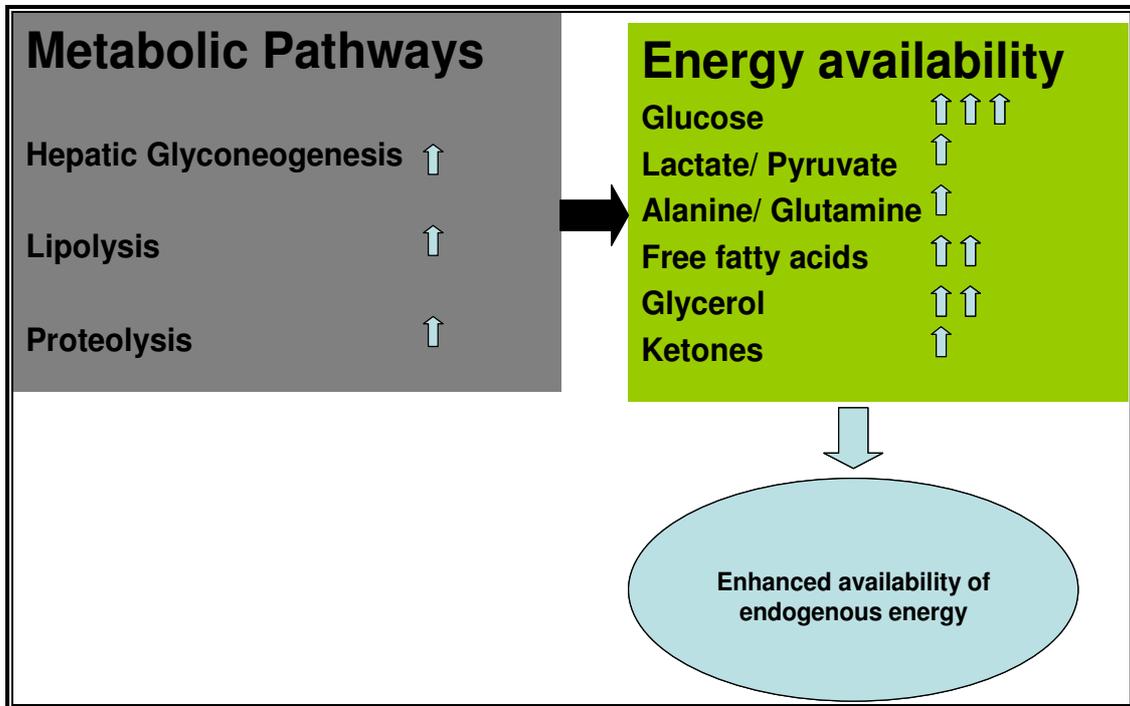
exogenous substrate supply. The overall aim of stress-induced catabolism is to use the endogenous fat and protein stores for the adequate provision of energy and glucose for glucose dependent tissues such as the brain, erythrocytes and immune system, and to release amino acids and nitrogen for the *de novo* synthesis of functional proteins, in particular acute phase proteins involved in the immune response. Both hunger and stress precipitate an imbalance between insulin and the counter regulatory hormones, in favour of the latter which results in catabolism (Figure. 1.4). During stress, unlike hunger metabolism, this imbalance is induced despite increased release of insulin, accompanied by a much higher increase of the catabolic insulin counter regulatory hormones, such as glucagon, cortisol and catecholamines. This is one of the main regulatory mechanisms for the difference in substrate utilization during hunger and stress. Another difference lies in the increased release of inflammatory mediators during stress enhancing catabolism, which is not the case during hunger.<sup>19</sup>



**Figure 1.4 Pattern of hormones and inflammatory mediators in stress and hunger metabolism**

(Source: Suchner U. 2003. <sup>21</sup>)

The characteristic features of stress-induced hypermetabolism, as determined by the neurological and hormonal responses to stress, are summarized in Figure 1.5.



**Figure 1.5 Characteristic features of hypermetabolism – determined by the neurological and hormonal response to stress**

(Source: Suchner U. 2003 <sup>21</sup>)

Stress-induced catabolism cannot be reversed through exogenous substrate supply. Nutrition therefore has to be adapted to the actual metabolic situation. The primary goal of nutrition during stress metabolism is the maintenance of organ and systemic functions, particularly that of the gut, liver, lung and the immune system. The goal should be to maintain not to restore lean body mass. Under stress conditions nutrition is also termed “metabolic support”.<sup>21 22</sup>

The amount of energy, fat and carbohydrates which needs to be administered to a critically ill patient has to be adapted to the actual metabolic capacity for substrate utilization and elimination. In practice this can be done through regular

control of plasma urea, plasma triglycerides and blood sugar, the regular calculation of the urea production rate and the regular determination of the respiratory quotient. These help in the recognition of metabolic changes and to prevent hyperalimentation, which has been shown to increase morbidity and mortality under the conditions of stress metabolism <sup>19</sup> .

The three phases of stress metabolism, as proposed by Cuthbertson, are still applicable and very helpful for establishing the preferred nutritional strategy.

The three phases of stress metabolism are phase 1 - the ebb phase, phase 2 - the flow phase and phase 3 -the convalescence phase (Figure.1.6) and can be described as follows:

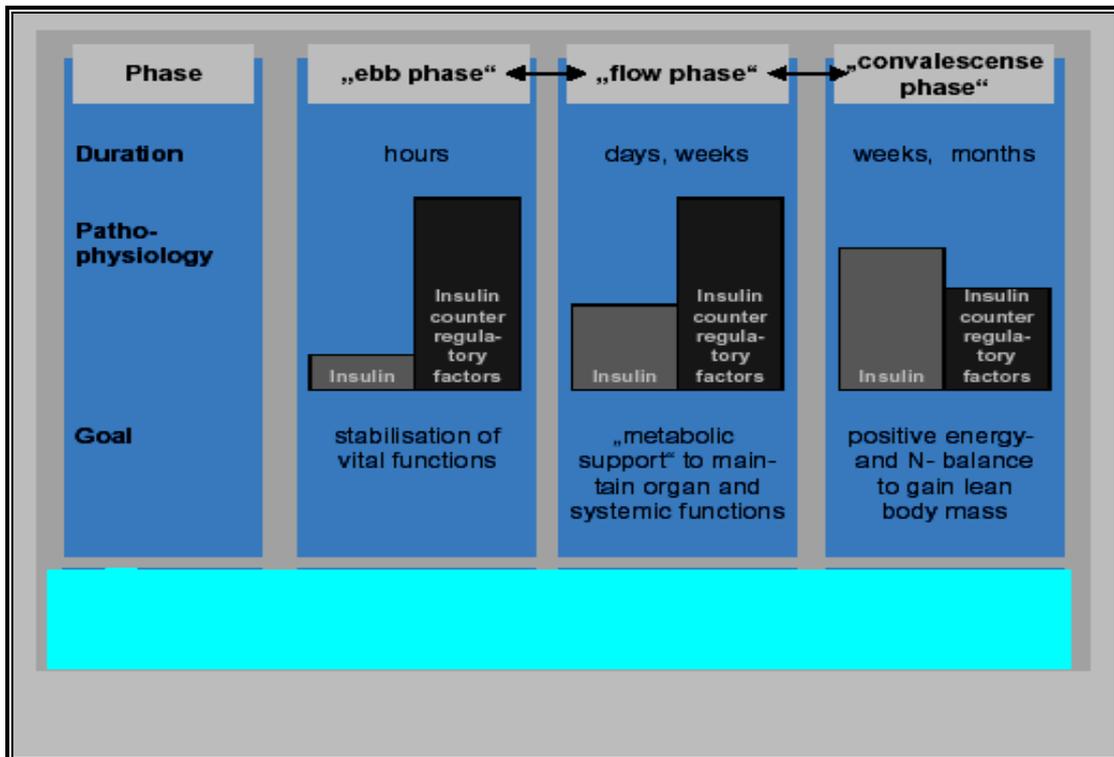


Figure 1.6 Phases of stress metabolism as defined by Cuthbertson and respective nutritional strategies (Source: Cuthbertson DP. 1978. <sup>23</sup>)

### **Phase 1 - Ebb phase / shock phase:**

The ebb phase, also known as the shock phase, follows immediately after trauma or the onset of severe infections and persists for a few hours, depending on the timing of resuscitation, i.e. respiratory support and hemodynamic stabilization of the patient. It develops anytime from minutes to approximately 24 hours after the insult. The insulin counter-regulatory factors dominate. The stabilization of vital functions, respiration, circulation and maintenance of organ functions is a priority. Nutrition is not indicated during the ebb phase.<sup>20 23</sup>

### **Phase 2 - Flow phase**

After resuscitation and stabilization of the patient, the flow phase predominates. This phase may last for several days or even weeks. The severity of it depends on the magnitude of injury and SIRS. Nutrition during this phase should focus on metabolic support and maintenance of organs and should therefore be carefully planned.<sup>20 23</sup>

### **Phase 3 - Convalescence phase**

The convalescence phase is only achieved after the stress-inducing causes have been cured. Only then will the anabolic insulin predominate over counter-regulatory factors. Positive energy and nitrogen balance can be achieved by providing adequate nutrition in order to gain lean body mass.<sup>20 23</sup>

The three phases do not necessarily follow each other. If stress inducing factors reappear or SIRS develops, the patient may fall back to the flow or even ebb phase. This may occur repeatedly and of course needs adaptation of the nutritional strategy to the respective metabolic situation.<sup>23</sup>

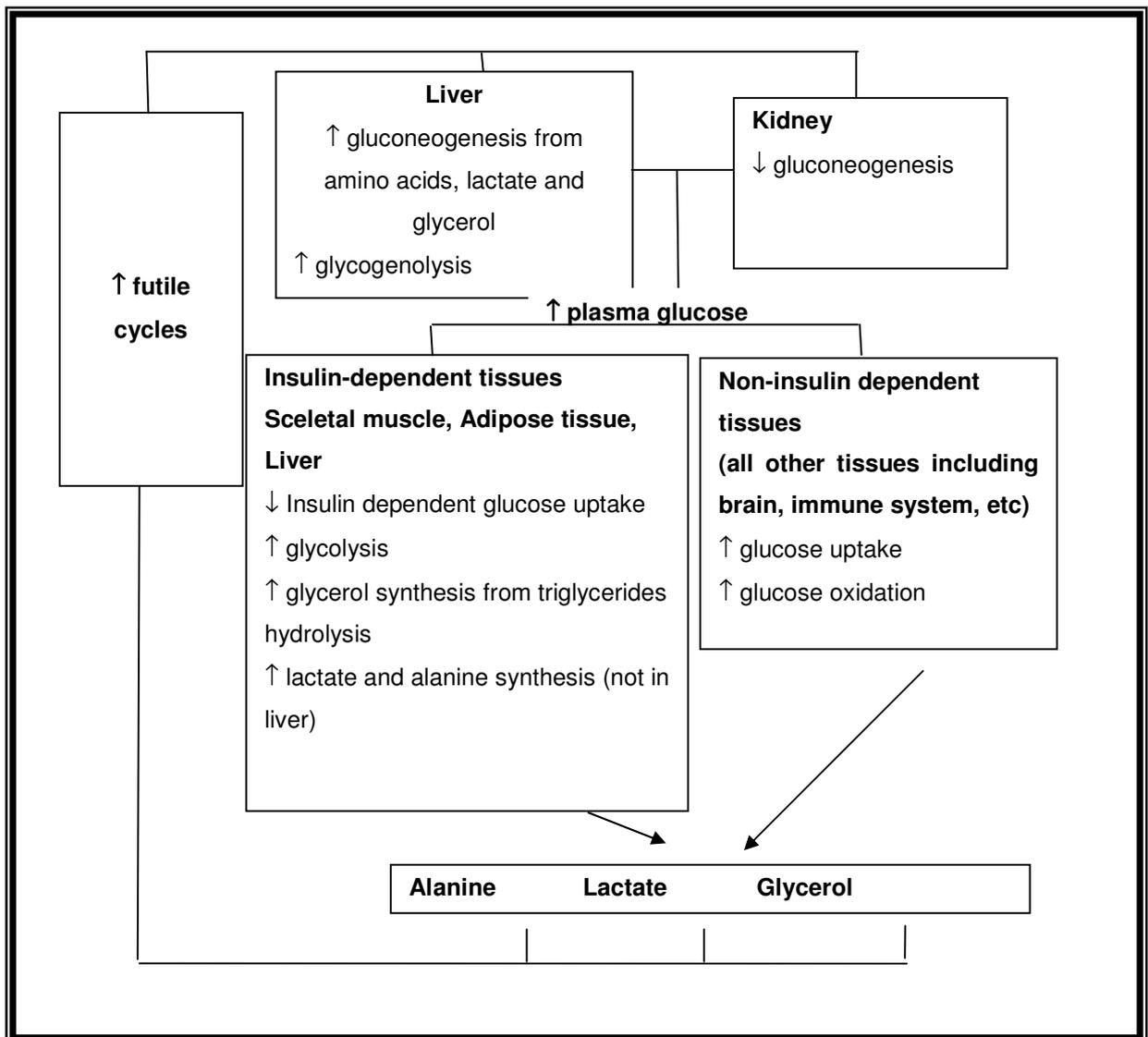
To better understand nutritional targets and interventions in these critically ill patients and to develop nutritional strategies which are expected to have a positive effect on the course of the illness, it is necessary to look more carefully at the ebb and flow phases and how these determine the metabolic immunological consequences and hence the course of the illness.

## **1.3 THE METABOLIC RESPONSE TO STRESS AND THE INTESTINAL DEFENSE SYSTEMS**

### **1.3.1 Metabolic Response to Stress**

The acute phase response to stress is probably designed to provide energy and substrates for protein synthesis and cell replication in visceral tissues ( i.e. liver, gut, immune cells and wound tissue) However during prolonged, intense stress, a severe depletion of body stores may adversely affect the morbidity and mortality of patients and delay the recovery from illness.<sup>20 23</sup>

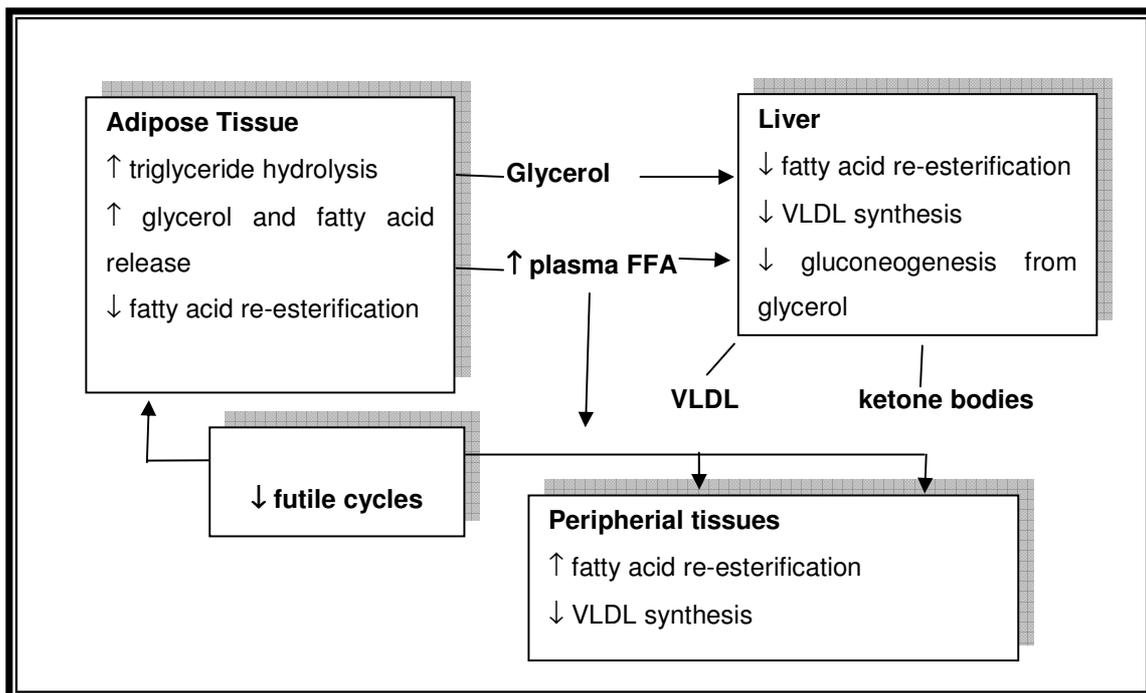
Critically ill patients experience a number of alterations in carbohydrate, lipid, amino-acid and protein metabolism (Figure 1.7 – 1.9). Hyperglycaemia during critical illness is caused by increased liver production of glucose and decreased glucose utilization in the skeletal muscles and the adipose tissue. The immune system, wound tissue, lung and skeletal muscles' accelerated pyruvate production is the result of an increased rate of glycolysis. The liver uses lactate, alanine and glycerol, derived from an accelerated lipolysis, as substrates for gluconeogenesis. Hypoxia or tissue hypoperfusion further accelerates lactate production (Figure 1.7).<sup>10</sup>



**Figure 1.7: Changes in glucose metabolism during critical illness**

(Source: Heyland DK et al. 2006. <sup>10</sup>)

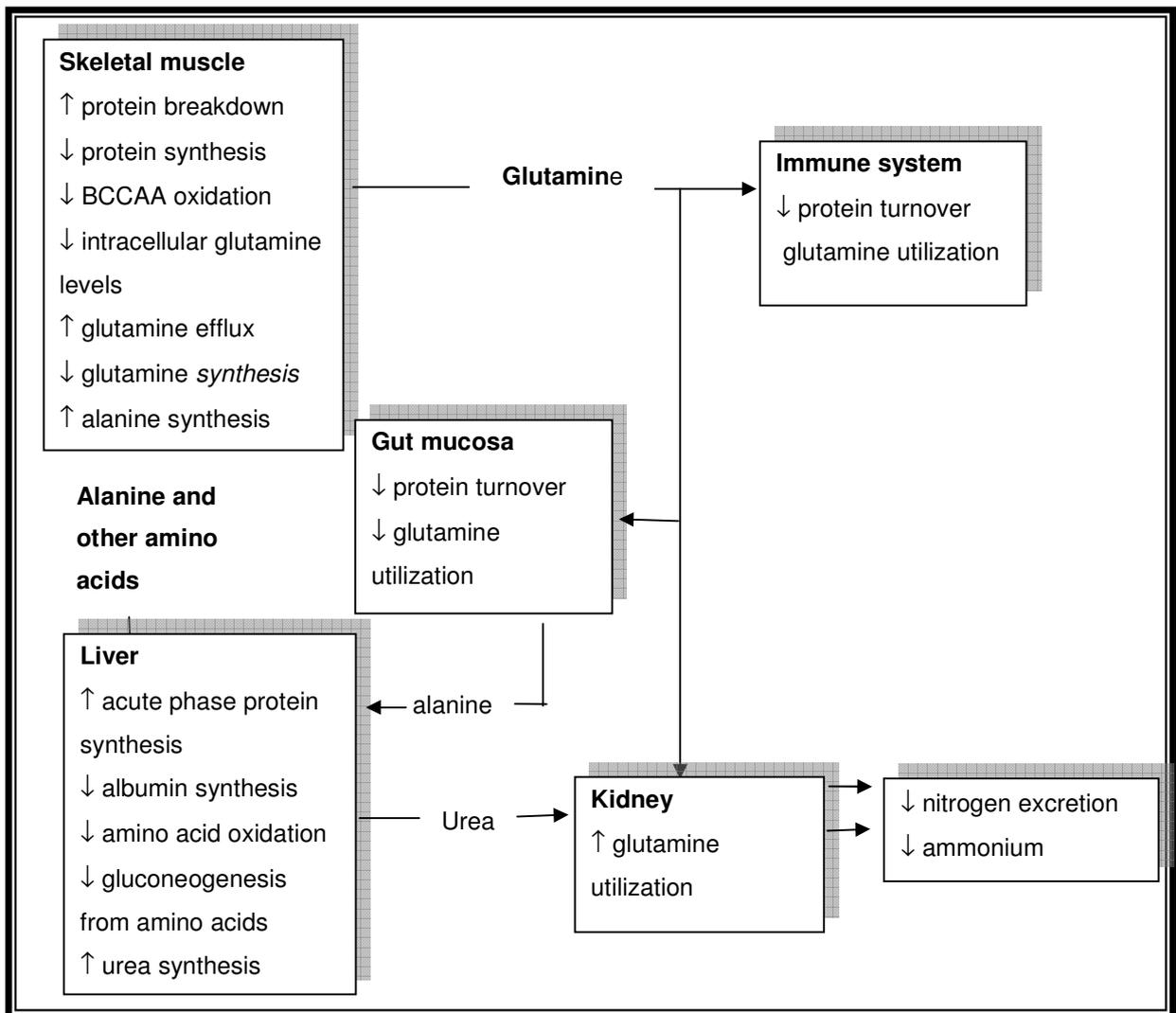
When nutritional support is insufficient for energy supply during critical illness, the endogenous lipids represent the main source of energy. In the adipose tissue, triglycerides (TGs) are hydrolysed to release free fatty acids (FFAs) and glycerol into the bloodstream. These increased FFAs result in depletion of intracellular TGs stores. Oxidation of FFAs in the peripheral tissue produces energy. The liver converts FFAs to ketones or re-esterifies FFAs to TGs which are released into the bloodstream as very low density lipoprotein (VLDL). Plasma FFA levels increase proportionately to the severity of the injury. (figure 1.8). <sup>10</sup>



**Figure 1.8 Lipid metabolism changes during critical illness**

(Source: Heyland DK et al. 2006. <sup>10</sup>)

Increased protein breakdown results in muscle mass loss. Glutamine is produced in the skeletal muscle which serves as a reservoir of free amino acids. Critically ill patients are characterized by a severe depletion of the intramuscular glutamine pool and an increased glutamine requirement in the gut, liver, kidney, immune system and wound tissue where glutamine is utilized as a major fuel for rapidly dividing cells. Glutamine also serves as a precursor for gluconeogenesis, nucleotide synthesis, ammonia excretion and glutathione formation. An increased rate of protein synthesis in visceral tissues partially compensates for the protein breakdown from skeletal muscle. The liver oxidizes excess amino acids and the muscle oxidizes the excess branched chain amino acids which the kidneys excrete as nitrogen. (figure 1.9) Muscle wasting leads to catabolism of the diaphragm, intercostal muscles, and heart, with increased risk of pulmonary complications from ineffective clearing of secretions. <sup>10</sup>



**Figure 1.9 Protein and amino acid metabolism changes during critical illness. (BCAA – Branched chain amino acids)**  
 (Source: Heyland DK et al. 2006. <sup>10</sup>)

These changes lead to increased energy requirement and protein catabolism and contribute to alterations in the immune system and gastrointestinal tract.

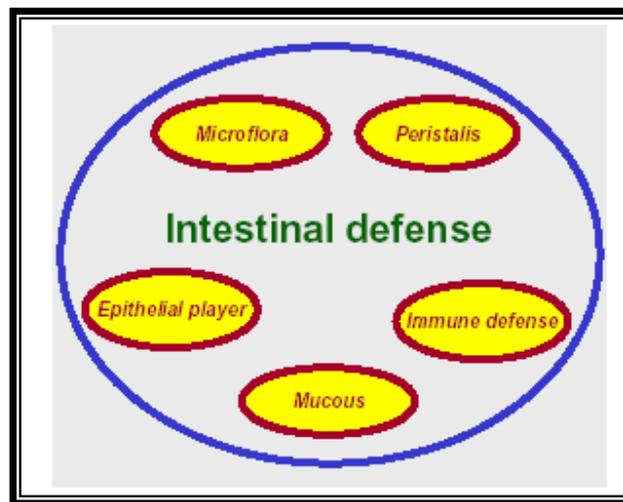
### 1.3.2 Intestinal Defense Systems

Beyond its digestive and absorptive capacities, the gastrointestinal tract is recognized for its immunological role and barrier function. Several studies have indicated that “bowel rest” ( when no enteral nutrition enters the digestive tract for a period of time) is associated with disruption of the mucosal barrier structure and

function, augmenting the inflammatory response to illness and resulting in greater infectious morbidity. Awareness of these associations and observations has led to the practice of providing early nutritional support to critically ill patients<sup>8 24</sup>

### 1.3.3 The Gastrointestinal Tract a Defense System

The gastrointestinal tract is usually considered as the organ for nutrient intake, nutrient digestion and absorption. There is, however, another extremely important role of the gastrointestinal tract which is its role in the overall host defense. (figure 1.10)<sup>12 23</sup>



**Figure 1.10 Components of Intestinal Defense**  
(Source: Vendemiale G et al. 1999<sup>12</sup>)

#### 1.3.3.1 Extrinsic defense mechanisms

In principle, all extrinsic mechanisms limit the number of antigens (pathogens), which may reach the mucosal surface, thus reducing the risk for invasion of the intestinal epithelium. These consist of luminal and epithelial surface defense mechanisms.<sup>30</sup>

Intestinal transit time is enhanced by peristalsis, limiting pathogen contact with the intestinal epithelium and subsequently possible pathogen adherence by preventing stasis in the gut.

The mucous coat is composed of mucin, a highly viscous glycoprotein that contains enzymes for digestion as well as IgA for bacterial neutralization. Mucin also carries many innate microbial defenses such as lactoferrin, defensins, peroxidases, and other potent low molecular weight antimicrobial inhibitors. When mucus is released into the gastrointestinal lumen the mucus stream draws micro-organisms away from the epithelial cells. In addition its viscous nature prevents adherence of micro-organisms to the intestinal epithelium.<sup>26</sup>

The physiological intestinal microflora protect against pathogenic bacteria by adhering to the intestinal epithelium, reducing the surface area for adherence of pathogenic bacteria and producing antimicrobial substances, such as fatty acids, and stimulating epithelial cell growth.<sup>26</sup>

IgA is the main immunological component of the extrinsic intestinal defense mechanisms. IgA is transported from the underlying gut-associated lymphoid tissue (GALT) into the intestinal lumen. It prevents invasion of pathogens by trapping micro-organisms, derived from the environment and food, in the mucous coat through formation of antigen-antibody complexes.<sup>26</sup>

### **1.3.3.2 Intrinsic defense mechanisms**

Pathogens that successfully escape the extrinsic defense mechanisms are confronted with the intrinsic defense barriers consisting of the mucosal epithelium and the GALT.

The mucosal epithelium provides various defense mechanisms. Tight junctions firmly connect the epithelial cells together, providing an effective mechanical barrier to pathogens.

Specialized epithelial cells produce mucus, antimicrobial substances or peptide hormones which contribute to the extrinsic surface defenses and intestinal immune response.<sup>23 26 56</sup>

GALT is the umbrella term for all lymphoid tissues located in the intestine, and the GALT lymphoid cells account for the estimated 80% of all immunoglobulin-producing cells of the body, which quantitatively underlines the importance of the gut for the overall immune response.

The GALT is composed of several unique immunological structures (Table 1). It plays an important role in the antigen specific immune response for the uptake and processing of antigens (pathogens) and the secretion of antibodies, in particular the IgA Error! Bookmark not defined.<sup>25</sup>

**Table 1.1 Immunological structures of the GALT**

<b>Organized lymphoid tissue in the lamina propria:</b>	<b>Unorganized lymphoid tissue:</b>
<ul style="list-style-type: none"> <li>▪ Peyer's patches</li> <li>▪ Appendix</li> <li>▪ Mesenteric lymph nodes</li> <li>▪ Solitary lymphoid nodules</li> </ul>	<ul style="list-style-type: none"> <li>▪ Intraepithelial lymphocytes</li> <li>▪ Lamina propria lymphocytes (primary site of IgA production)</li> </ul>

The Peyer's Patches are the site where the antigen specific immune response is initiated. After a complex process of cell maturation, lymphocytes are primed to become either IgA secreting plasma cells or to produce cytokines regulating the IgA secretion from the plasma cells.<sup>5 26 27</sup>

This summary of intestinal defense demonstrates the major role the gut plays in the overall host defense of the body. Disintegration of the intestinal barrier under pathological conditions, as is the case in critical illness, will clearly have deleterious effects. Thus it becomes obvious that every effort should be made to

prevent the breakdown of the intestinal defense barriers in critical illness. To guarantee this adequate nutrition route and type of nutrition is of the utmost importance.

## **1.4 THE GASTROINTESTINAL TRACT IN CRITICAL ILLNESS**

It is generally assumed that gut dysfunction occurs early in shock, sepsis and following trauma and that gut failure and mucosal injury is an unfavourable prognostic factor in critically ill patients.<sup>28</sup>

The following changes are all seen to a variable extent as part of gut dysfunction:

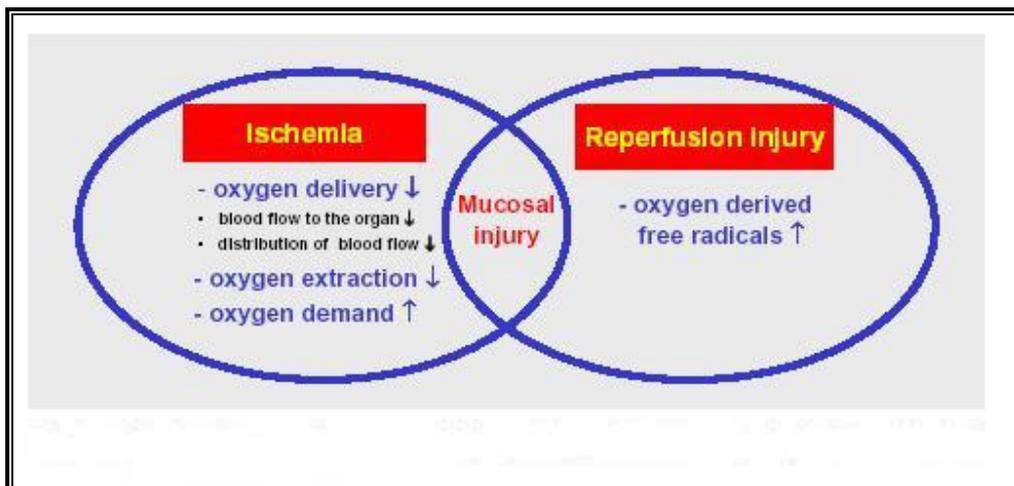
- mucosal injury
- increased intestinal permeability
- disturbed immune functions of the GALT
- bacterial overgrowth
- motility disorders
- ileus
- malabsorption

### **1.4.1 Mucosal Injury**

The role of the “canary of the body”, has been attributed to the gut, which means that it is a sentinel organ that is particularly susceptible to the interruption of blood flow or oxygen and substrate supply.<sup>9,20</sup>

Mucosal injury results in increased intestinal permeability and/or the release of inflammatory or other toxic substances from the damaged mucosa.<sup>29</sup>

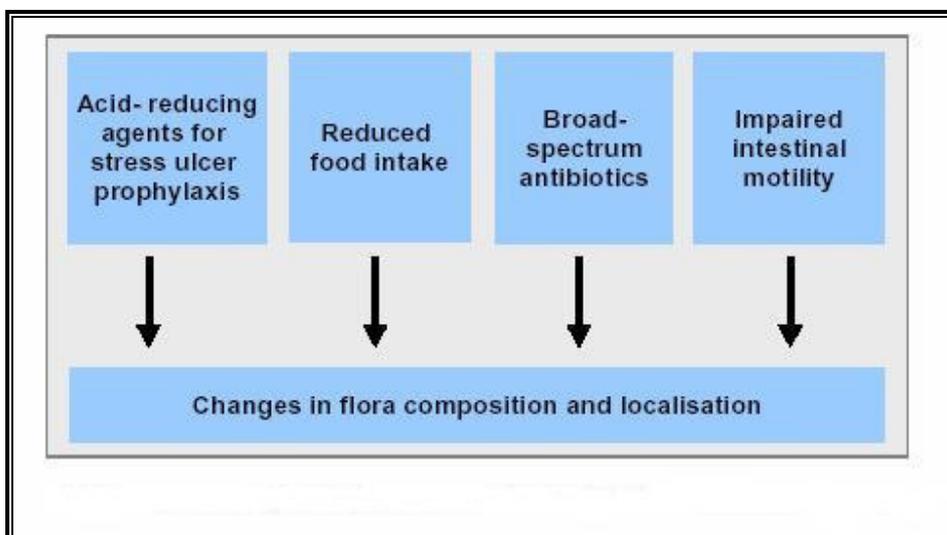
The function of the gut as a barrier can weaken after mucosal injury due to ischaemia and reperfusion injury. (figure 1.11)<sup>20</sup>



**Figure 1.11 Mechanisms causing mucosal injury during critical illness**  
 (Source: Heyland DK, Samis A. 2003 <sup>29</sup>)

#### 1.4.2 Bacterial Overgrowth

A further problem in critically ill patients is the colonization of the upper gastrointestinal tract with bacteria and/or fungi otherwise known as “bacterial overgrowth”. Not only the localization, but also the composition of the flora is frequently changed during critical illness (Figure 1.12).



**Figure 1.12 Main reasons for bacterial overgrowth in critically ill patients**  
 (Source: HeylandDK, Samis A. 2003 <sup>29</sup>)

Colonisation of the upper GIT occurs with the same species that cause nosocomial infections. Descriptive studies have shown that bacterial overgrowth is a risk factor for ICU-acquired infection by either aspiration or translocation.<sup>30 31</sup>

### 1.4.3 Motility Disorders

Adequate gastrointestinal motility is essential for proper transport, digestion and absorption of nutrients. Motility disorders are a limiting factor for the delivery and success of enteral nutrition.<sup>32</sup>

In the critically ill patient, gastrointestinal motility is often impaired due to multiple factors as shown in Table 1.2.<sup>33</sup>

**Table 1.2 Factors which may disturb gastrointestinal motility in critical illness**

Factors	For Example
• <b>Underlying diseases / insults:</b>	Head injury, Burns, Extensive abdominal surgery / trauma, Pancreatitis, Diabetes mellitus, Intestinal pseudo-obstruction
• <b>Metabolic abnormalities</b>	Hyperglycemia, Hypopotassemia
• <b>Drugs</b>	Opiates,(mechanical venatilation), Erythromycin, Anticholinergics
• <b>Stress</b>	Pain, Sepsis
• <b>Ischaemia</b>	
• <b>Excessive NO</b>	

Slow gastric emptying is most common in critically ill patients. The prevalence can be up to 80% in these patients. Abnormal gastric emptying is the most important consequence of intolerance to naso-gastric delivery of food. Common symptoms are abdominal pain, bloating, nausea and vomiting which may result in aspiration pneumonia<sup>33</sup>

In 20% of critically ill patients small intestinal motor dysfunction also occurs, as critically ill patients commonly develop abdominal cramps and diarrhoea with duodenally delivered feeds.<sup>33</sup> The incidence of intolerance to early jejunal feeding ranges from 13% to 37%.<sup>34</sup> Tournadre et al have found small intestinal motility disorders in 100% of patients after major abdominal surgery. Duodenal and jejunal motor activity occurred within 2 hours of surgery, but with a higher frequency and abnormal migration compared to healthy subjects. When nutrients were infused into the duodenum, the motility pattern was not normalized.<sup>33</sup>

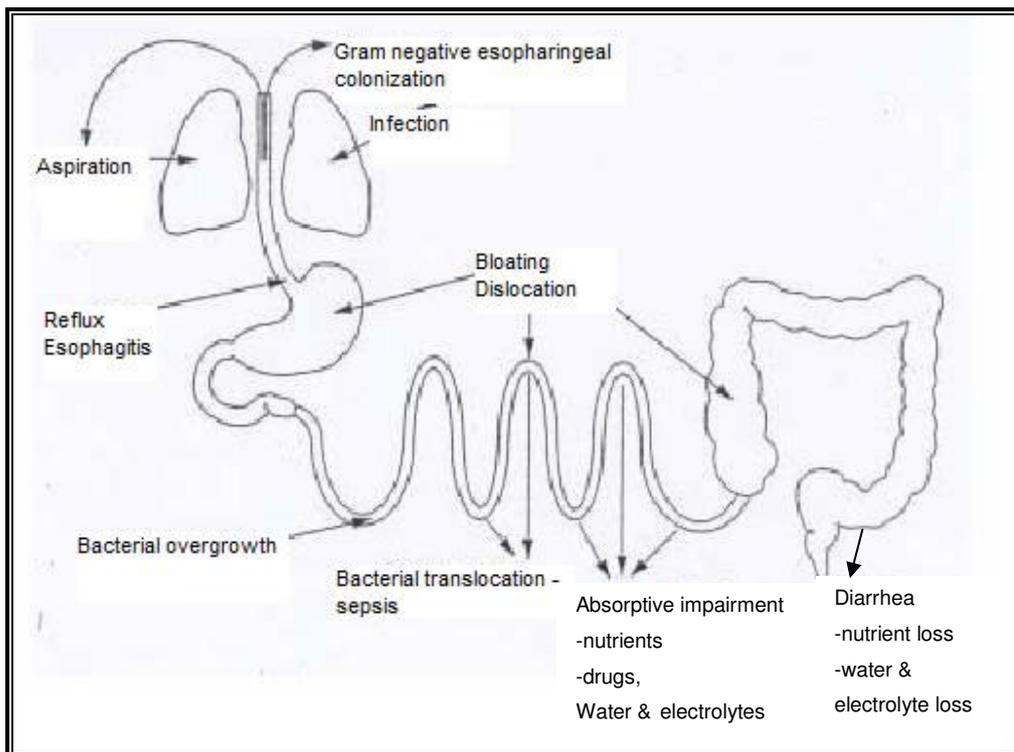
Postoperative ileus occurs to some degree after any abdominal surgery but also after several extra-abdominal operations. Ileus is defined as an inhibition of the propulsive intestinal motility.<sup>13</sup>

The possible consequences of gastrointestinal motility disorders are shown in (Figure 1.13).

Absorptive impairment

-nutrients

-drugs, water & electrolytes



**Figure 1.13 Consequences of GI motility disorders in critically ill patients**  
 (Source: Salloum RH et al. 1991<sup>34</sup>)

Motility disorders in critically ill patients are difficult to rectify. Delayed gastric emptying can be overcome by administering enteral feeds into the small intestine (nasojunal feeding) and/or the administration of propulsive drugs.<sup>34 34</sup>

#### 1.4.5 Malabsorption

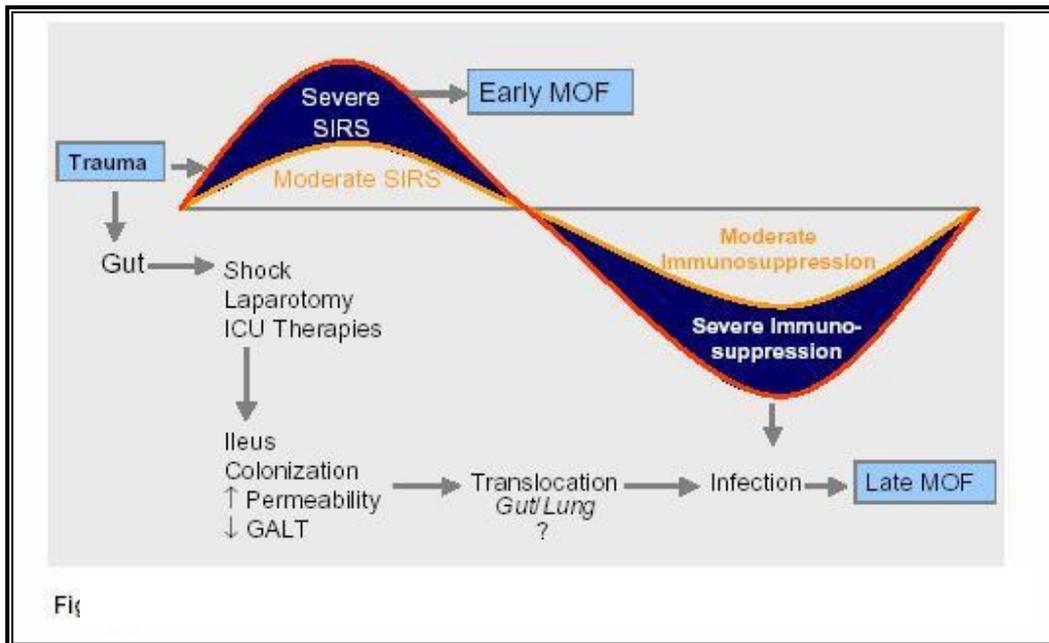
The intestinal uptake of certain amino acids and sugars seems to be lower in septic patients.<sup>34 35</sup> With regard to glutamine, it seems that regulation by hormones ensures the uptake of this very important fuel for the intestinal mucosa.<sup>36</sup> Lipid absorption is severely decreased after trauma, hemorrhage and resuscitation.<sup>36</sup>

Multiple factors contribute to the malabsorption of enterally administered nutrients in the critically ill patients for example:

- Hypoperfusion of the mucosa
- Mucosal injury
- Bacterial overgrowth
- Motility disorders
- Drugs
- Impaired exocrine pancreatic functions.<sup>37 38</sup>

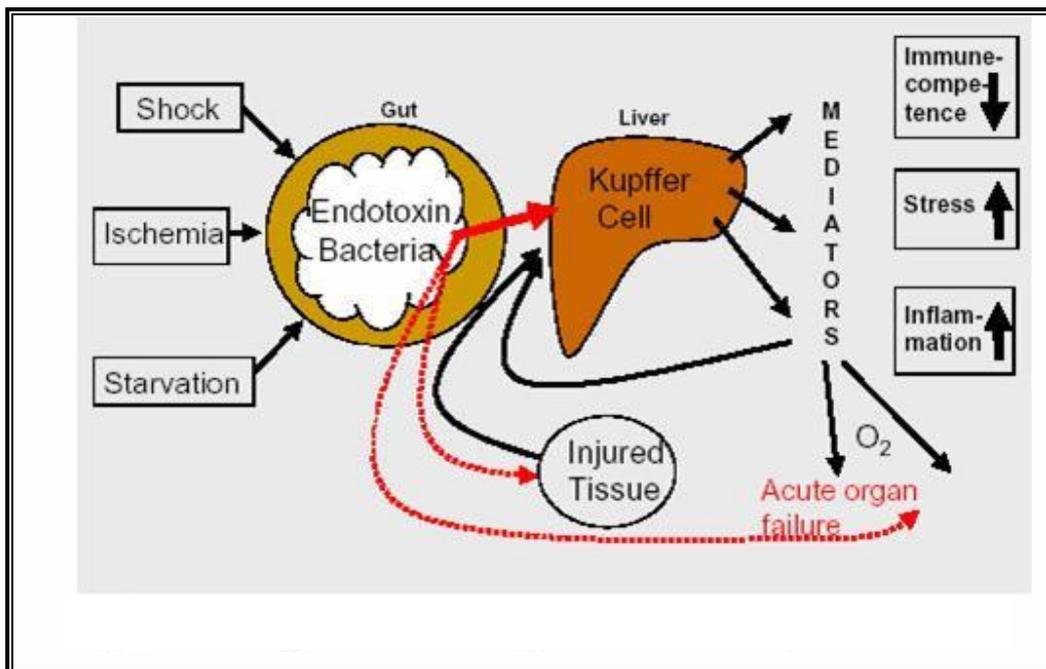
#### **1.4.6 The Gut as the Starter and/ or Motor of Multiple Organ Failure (MOF)**

Infection is the most common cause of mortality and morbidity in critically ill patients.<sup>45</sup> It has been suggested that the gut is involved in the pathogenesis of many nosocomial infections and possibly SIRS and MOF. However, the exact mechanisms and the correlation between gut failure and MOF remain elusive.<sup>9</sup> It has been hypothesized that gut failure is a key factor in the development of late (secondary) MOF in critically ill patients after polytrauma and shock. Above all, the loss of the very important immunological and mechanical barrier function seems to be correlated with the development of systemic infection and inflammation. (Figure 1.14).<sup>9</sup>



**Figure 1.14 Hypothesized role of the gut in post-injury MOF**  
 (Source: Moore FA. 2000<sup>39</sup>)

It is assumed that the gut may be an entry point for infectious bacteria and toxins into the blood, a phenomenon which is called “bacterial translocation”. The bacteria and toxins which have migrated through the gut mucosa reach other organs like the liver and the lung via blood and lymph. Stress hormones, free radicals and inflammation-promoting mediators like cytokines are released as a reaction to the invasion by pathogens. A regular cascade of inflammatory processes may result in hyperinflammation, severe organ malfunction and failure. (Figure 1.15).<sup>4 39</sup>



**Figure 1.15 Hypothesized role of the gut and liver in the development of MOF (Source: Nieuwenhuijzen GA, Goris JA. 1999<sup>40</sup>)**

There is a great deal of laboratory data identifying bacterial or endotoxin translocation as a key factor in sepsis and SIRS. Although clinical evidence is outstanding, it is generally believed that bacterial translocation also occurs in critically ill patients and was demonstrated in a study in burn patients.<sup>41, 42, 43, 44</sup>

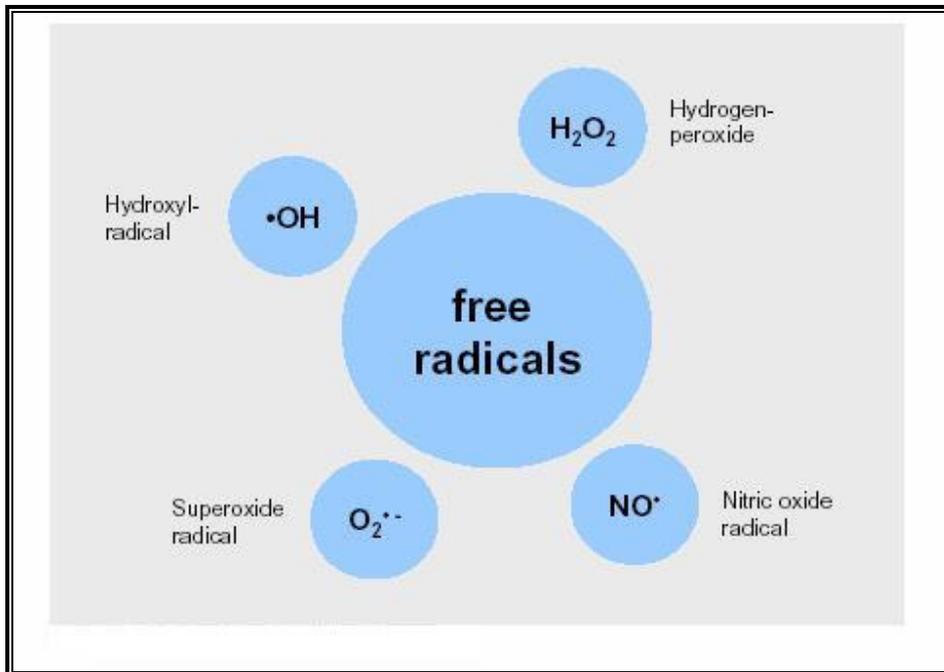
Approaches designed to diminish gut permeability early in critically ill patients may improve clinical outcome and survival in these patients.<sup>45</sup>

## 1.5 DEPLETION OF KEY NUTRIENTS

### 1.5.1 Oxidative Stress

Oxygen is often referred to as a “double-edged sword”. Although it is absolutely critical to life, many essential intracellular reactions, for which it is required, result in the formation of oxygen free radicals (OFR). OFRs, superoxide radical, hydrogen peroxide, nitric oxide and hydroxyl radical, are molecules which have one or two unpaired electrons, making them extremely unstable, highly reactive

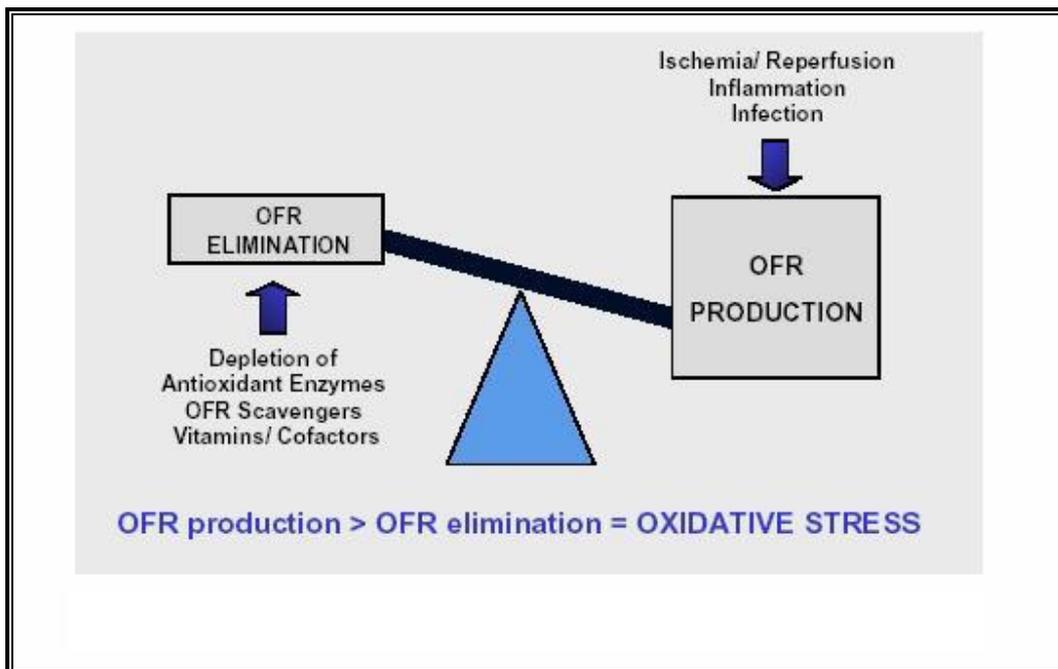
and thus potentially toxic to cell membranes, proteins, and deoxyribonucleic acid (DNA).<sup>46</sup> (Figure 1.16).



**Figure 1.16 Clinically relevant free radicals**

(Source: Jacob RA, Burri BJ. 1996<sup>46</sup>)

Under normal circumstances, our body is protected against this oxidative challenge by natural defense systems such as radical scavenging enzymes or vitamins.<sup>47</sup> When the balance (Figure 1.17) between these protective antioxidant mechanisms and the generation of OFRs is disturbed, we encounter a situation called “oxidative stress”.<sup>48</sup> In critical illness, there is an imbalance of increased OFR production (during ischemia/reperfusion, inflammation and/or infection) and diminished OFR elimination because of a depletion of endogenous antioxidants. This may be compounded by pre-existing factors such as age, smoking, malnutrition as well as chronic diseases, such as atherosclerosis, diabetes mellitus or rheumatoid arthritis. These conditions are all associated with an increased production of OFRs or decreased antioxidant capacity or both.



**Figure 1.17 Imbalance of oxygen free radical production and elimination in critical illness**

(Source: Garvin CG, Brown RO. 2001 <sup>42</sup>)

### 1.5.2 Development of oxidative stress in critical illness

Oxidative stress plays a major role in the pathophysiological processes (ischemia/reperfusion injury, inflammation, infection) induced by critical illness. Various mechanisms contribute to this association. <sup>47</sup>

#### 1.5.2.1 Ischemia/reperfusion injury

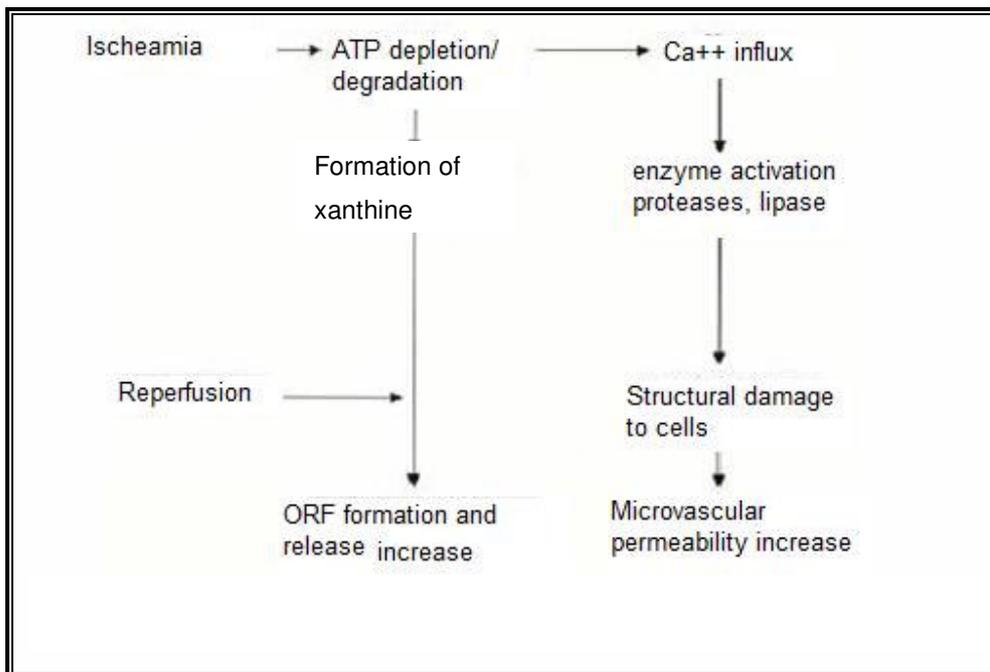
Tissue ischemia, hypoperfusion followed by reperfusion, represents a major mechanism by which OFRs are generated in critical illness. The intestinal mucosa are some of the most sensitive tissues to ischemia <sup>47</sup>

When oxygen availability is limited in the tissue of vital organs by hypoperfusion, the cells shift from aerobic to anaerobic metabolism.

When cells cannot maintain adequate energy production, they compensate for this by breaking down existing ATP. Consequently an influx of  $\text{Ca}^{2+}$  ions into the cells becomes possible. Increased intracellular calcium activates different enzymes, all of which may destroy structural cell components. Under conditions of ischemia the enzyme, xanthine oxidase, is activated. (figure 1.18).<sup>43</sup>

Reperfusion means the restoration of normal blood flow in tissues and organs. Early on during reperfusion of ischemic tissue, a great number of OFRs are generated mainly by the activity of xanthine oxidase in the cells.

One of these OFRs, the hydroxyl radical, is especially toxic as it is the most reactive OFR. This hydroxyl radical is so reactive that it attacks all biological substances such as proteins, polysaccharides, nucleic acids (resulting in DNA strand breakage) and polyunsaturated fatty acids.<sup>52</sup>



**Figure 1.18 Important pathophysiological mechanisms by which ischemia and reperfusion lead to OFR release and cellular damage (Source: Barber DA, Harris SR 1994<sup>52</sup>)**

### **1.5.2.2 inflammatory response to oxidative stress**

The inflammatory response to critical illness involves the activation of leukocytes and other inflammatory cells, leading to a production of reactive oxygen species. These species can damage most cellular structures including DNA, proteins and lipids, and can become harmful to the patient when the endogenous antioxidant defense mechanisms are overwhelmed.<sup>49</sup>

It is therefore hypothesized that ischemia/reperfusion after surgery, severe trauma or infection produces OFR-driven tissue injury and induces an inflammatory response in other, remote organs and tissues.

Inflammation itself stimulates the generation of OFRs and creates a vicious cycle.

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### **1.5.3 Antioxidant Mechanisms**

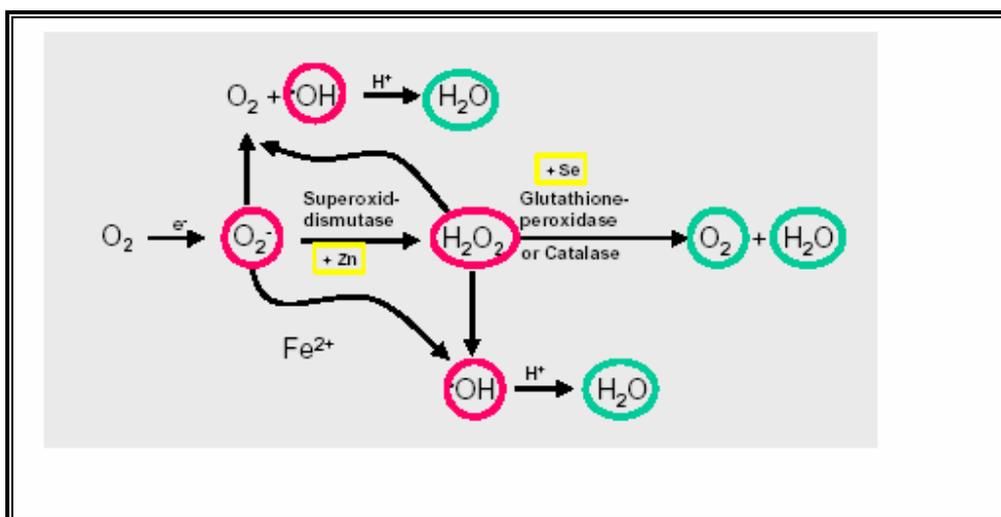
Our organism maintains a complex endogenous defense system against OFRs. As a matter of fact, a variety of extra and intracellular antioxidant defense systems work together, involving the following components:

- Antioxidant enzymes, i.e. superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase
- Sulfhydryl group donors, i.e. glutathione
- Antioxidant vitamins E, C,  $\beta$ -carotene

The first line of intracellular defense consists of a group of antioxidant enzymes. When these enzymatic antioxidants are overwhelmed, OFRs are free to react with susceptible target molecules within the cell, like fatty acids in the cell membrane. The second line of defense is the scavenging of OFRs by non-enzymatic antioxidants which are water soluble, such as glutathione and vitamin C, or lipid soluble such as vitamin E and  $\beta$ -carotene.<sup>50</sup>

### 1.5.3.1 Antioxidant enzymes

Enzymes directly involved in the intracellular detoxification of OFRs are superoxide dismutase, catalase, and glutathione peroxidases<sup>51</sup>. Indirect antioxidant functions are also mediated by enzymes such as glutathione reductase, which restores endogenous antioxidant levels as shown in Figure 1.19.<sup>52</sup>



**Figure 1.19 Enzymatic elimination of oxygen free radicals**  
(Source: Barber DA, Harris SR 1994<sup>52</sup>)

The trace minerals selenium and zinc are also essential cofactors for some of the antioxidant enzymes.

**Selenium:** Selenium is a component of a family of about 35 selenoproteins, some of which have important enzymatic functions. Important selenium-dependent enzymes include the family of glutathione peroxidases, which reduce hydrogen peroxide to water and convert lipid and phospholipid hydroperoxides to harmless alcohols, and thioredoxin reductase which helps to control the cellular redox status.<sup>7</sup>

#### **Zinc:**

Zinc is present in the Cu-Zn form of superoxide dismutase<sup>7</sup>

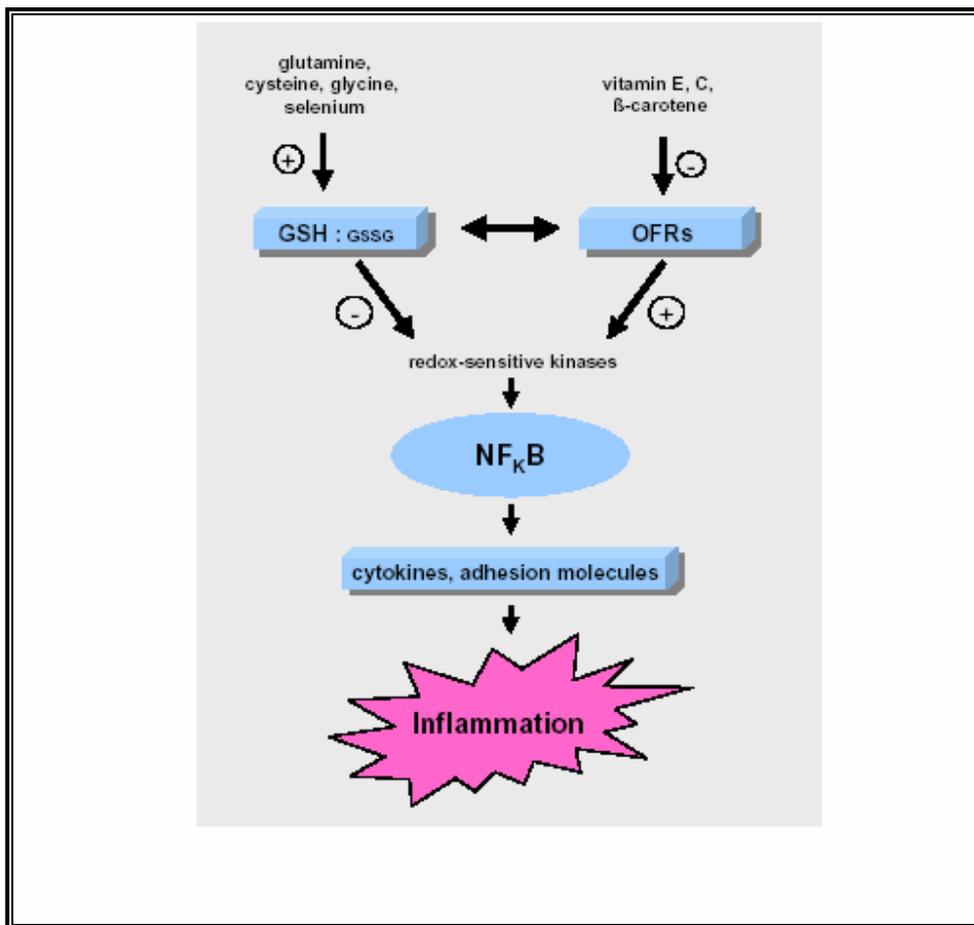
### **1.5.3.2      Sulfhydryl group donors**

#### **Glutathione:**

Glutathione is a tripeptide consisting of the three amino acids glutamine, cysteine and glycine. Glutathione is predominantly synthesized in the liver from where it can be exported to other organs. Recent information suggests that glutathione can also be synthesized in a number of other tissues.

The glutathione synthesis depends on the availability of the precursors glutamine, cysteine and glycine. Intracellularly, glutathione is quantitatively the most important endogenous antioxidant and radical scavenger. Glutathione is present mainly in the reduced, monomeric form (GSH) and, at far lower concentrations, in the oxidized, dimeric form (GSSG).

The ratio of GSH to GSSG is the most important regulator of the redox potential in the cells. This GSH redox status is critical for various biological events including gene activation, regulation of cell proliferation, apoptosis and inflammation. (figure 1.20).



**Figure 1.20 Redox-regulated activation of NF  $\alpha\beta$  as a presentation of the formation of pro-inflammatory mediators**  
 (Source: Roth E et al. 2002<sup>53</sup>)

It also has antioxidant activity by reacting with the extremely destructive hydroxyl radical that attacks all cellular components.<sup>53</sup>

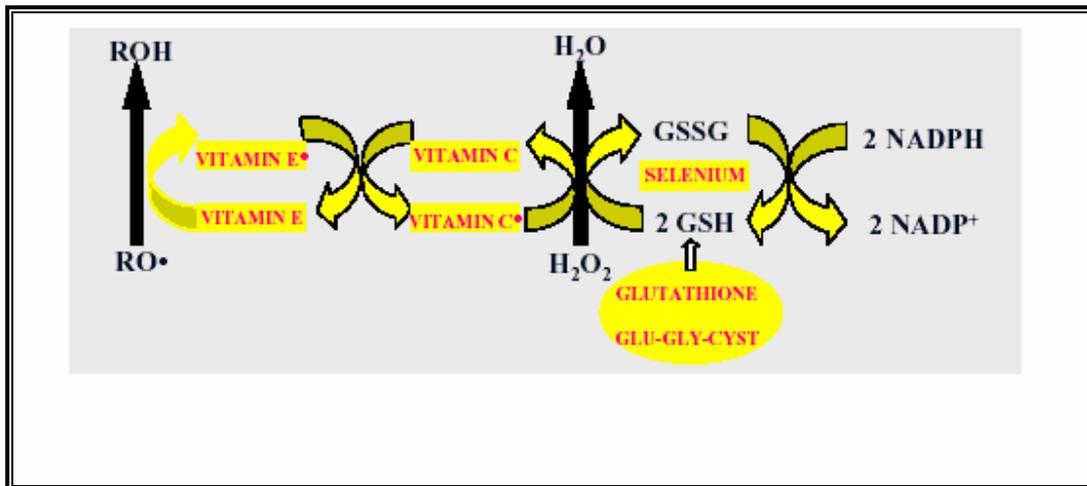
### **Vitamin Antioxidants**

**Vitamin C:** Ascorbic acid is the predominant water-soluble antioxidant in the body. Vitamin C has two primary antioxidant functions: First vitamin C reacts with and inactivates OFRs in the water-soluble compartments of the body, the cytosol, plasma, and extracellular space. Secondly and perhaps equally important, vitamin C regenerates oxidized vitamin E..<sup>52</sup>

**Vitamin E:** Vitamin E is a mixture of closely related compounds called tocopherols and  $\alpha$ -tocopherol is the most potent. Vitamin E is highly lipid soluble and is therefore distributed primarily in cell membranes and lipoproteins where it acts to interrupt free radical chain reactions such as lipid peroxidation. By reacting with free radicals, a non-reactive Vitamin E radical is formed. This “spent” form of vitamin E is then reactivated to its original state by interaction with vitamin C and glutathione.<sup>52</sup>

**Beta-carotene:**  $\beta$ -carotene is a pigment found in all plants and is the major precursor of vitamin A. Like  $\alpha$ -tocopherol,  $\beta$ -carotene is a lipid soluble substance.  $\beta$ -carotene is a very effective quencher of singlet oxygen and also inhibits lipid peroxidation. Interestingly, it seems to be especially effective under low oxygen tension (ischemia).<sup>52</sup>

The interactions of vitamin C, E, selenium and glutathione are very important in order to maintain the antioxidant defenses in the body. All of these antioxidants act synergistically. (Figure 1.21) The tocopherol radical reacts with vitamin C to regenerate vitamin E. The vitamin C radical is then enzymatically reduced back to vitamin C via the selenium-dependent glutathione peroxidase.  $H_2O_2$  is converted to water at the same time. The oxidised glutathione (GSSG) is reduced to GSH in the presence of NADPH.



**Figure 1.21 Interactions of vitamins E and C, selenium and glutathione to maintain antioxidant defenses**

(Source: Johnson CD, Kudsk KA. 1999)

It appears that the best antioxidant defense against OFRs and their inflammatory consequences involves synergistic efforts of all intra- and extracellular antioxidants available in our body.

#### 1.5.4 Antioxidant Depletion In Critical Illness

Oxidative stress plays a major role in the pathophysiological processes (ischaemia/reperfusion injury, inflammation, infection) induced by critical illness leading to a high consumption of antioxidants<sup>50</sup>.

Hypermetabolism associated with injury and inflammation (infection) is inevitably linked with an increased demand for nutrients including the antioxidant vitamins and trace elements.<sup>54</sup>

Critically ill patients are likely to lose substantial amounts of antioxidant micronutrients. Losses may be considerable after burns (since burns exudate fluid), in patients with large blood loss (haemorrhagic shock), in those who require renal replacement therapy such as hemodialysis or hemofiltration

following acute renal failure and in patients with postoperative complications leading to gastric aspirate or intestinal fistula losses.<sup>55</sup>

Additionally, pre-existing factors can contribute to the oxidative stress and consequently the depletion of antioxidants in critically ill patients. Last but not least, the adequate nutrient supply is often delayed or interrupted in critically ill patients.<sup>56</sup>

Table 1.3 summarizes the factors which contribute to a depletion of antioxidants in critically ill patients.

**Table 1.3 Predisposing factors for depletion of antioxidants in critically ill patients**

Pre-existing deficiencies: - due to old age, smoking, malnutrition, chronic diseases
Increased requirements: - high antioxidant consumption from high radical formation - high demands from hypermetabolism
Increased losses: - skin exudate in burns, blood losses, dialysis, gastric aspirate, intestinal fistula
Reduced supply: - post-traumatic , postoperative delay of adequate nutrition/ antioxidant supply - interruptions in nutrient supply because of clinical/diagnostic procedures

Many studies have demonstrated low plasma and intracellular concentrations of the various antioxidants in critically ill patients. The antioxidant levels in critically ill patients decrease rapidly after the insult, trauma or surgery and stay below normal levels for several days or even weeks.

In one study, in patients with SIRS, plasma levels of  $\alpha$ -tocopherol,  $\beta$ -carotene, ascorbate and selenium were significantly lower compared to a (healthy) control

group even on the day of admission. Normal levels were not reached during 6 days in spite of a parenteral supply of antioxidant micronutrients (average daily doses: 9.1 mg vitamin E, 100-500mg vitamin C, 120 µg selenium). The levels remained severely depressed for β-carotene which was not included in the TPN. The plasma levels of lipid peroxidation products, as a marker of massive oxidative stress, increased significantly at the same time<sup>2</sup>. In another study the plasma antioxidant potential in patients with severe sepsis was initially decreased (< 18 hours) and failed to return to normal before day 6. Continuously low levels (up to day 12) of α-tocopherol and β-carotene were strongly associated with a higher mortality rate<sup>57</sup>. Berger et al<sup>58</sup> measured serum selenium levels below normal for up to 20 days in burn patients. Glutathione peroxidase was also depressed for 20 days, indicating a deficiency state in these patients. Selenium levels remained depressed for more than two weeks in patients with SIRS.<sup>80 59</sup>

In severely ill patients with SIRS and sepsis, a significant negative correlation was found at the time of admission between plasma selenium concentration and APACHE II score (which is an indicator for the severity of the illness).. In sepsis patients, mean plasma selenium concentration was negatively correlated with the severity of sepsis.<sup>60</sup>

Bertin-Maghit et al (2000) evaluated the time frame of oxidative stress in burn patients. They found an immediate decrease in plasma levels of antioxidant vitamins and trace elements, as well as diminished antioxidant enzyme activities on day 1. There was a significant increase in end-products of lipid peroxidation at the same time. This oxidative stress appeared to be sustained, lasting at least for the whole observation period of 5 days in this study.<sup>61</sup> The inadequate availability of antioxidant vitamins and trace elements, in a phase of overwhelming production of toxic free radicals, severely enhances oxidative stress in critically ill patients. The oxidative damage to cells and tissues and an increase in the production of pro-inflammatory cytokines are the consequences. The consequent dramatic imbalance of pro- and antioxidants plays a role in the pathogenesis of multiple organ dysfunction.

Furthermore the deficiency of vitamins and trace elements can impair the immune functions with increased likelihood of infectious complications in these patients<sup>5</sup> Thus, injury and inflammation cause significant decreases in serum antioxidants and antioxidant potential, to counteract oxidative stress in critically ill patients immediately after trauma or surgery.

The sicker the patient is, the larger the depletion of antioxidants. Very early provision of antioxidant micronutrients (within the first 24 hours) may thus be beneficial in highly stressed patients.<sup>62</sup>

### **1.5.5 Antioxidant Replacement**

The question arises, how much antioxidant replacement or supplementation should critically ill patients receive?

Because of the factors which are dependent on many individual conditions (nutritional status of the patient, underlying disease, cause and kind of critical illness), it is impossible to predict the exact requirement of antioxidants for an individual patient. The amounts of antioxidant vitamins and trace elements in common TPN or TEN solutions, for critically ill patients, probably meet the minimum dietary recommendations for preventing deficiency. However, in terms of meeting the higher demands in these patients, the use of supplemental therapeutic concentrations of antioxidants is likely to be required<sup>63</sup>. However the optimal therapeutic doses of antioxidant therapies for critically ill patients are still unknown.<sup>47</sup>

Neither official authorities nor nutrition societies have established recommendations for the antioxidant supply to critically ill patients to date. Only a few quantitative recommendations have been suggested in the literature (Table 1.4).

**Table 1.4 Recommendations for the antioxidant supplementation of critically ill patients from current literature**

<b>Per Day</b>	<b><i>Galban Rodriquez (2000)**</i></b>	<b><i>Berger &amp; Shenkin (2000)*</i></b>	<b><i>Borhani &amp; Helton (2000)**</i></b>
<b><i>Vit A</i></b>	<b><i>3.3 mg</i></b> (better in $\beta$ -carotene form)	<b><i>1-2 mg</i></b>	
<b><i>Vit E</i></b>	<b><i>364 – 910 mg</i></b>	<b><i>10 200 mg</i></b>	<b><i>910 mg</i></b>
<b><i>Vit C</i></b>	<b><i>2000 mg</i></b>	<b><i>250 -&gt; 1000mg</i></b>	<b><i>&gt; 1000mg</i></b>
<b><i>Selenium</i></b>	<b><i>100<math>\mu</math>g</i></b>	<b><i>100 – 500 <math>\mu</math>g</i></b>	
<b><i>Zinc</i></b>	<b><i>50 mg</i></b>	<b><i>10 – 40 mg</i></b>	

\* recommendations for parenteral supply

\*\* no recommendations for route of administration

**Tabel 1.5 Changes of key antioxidant parameters in critical illness**

Critical Illness	Antioxidant Parameter	Effect	References
<b>ARDS Adult Respiratory Distress syndrome</b>	Vit E β-carotene Vit C Selenium	↓	Cross et al. 1990 Richard et al. 1990 Nakae et al. 1995 Metnitz et al. 1999
<b>Sepsis and septic shock</b>	Antioxidant potential Vit E β-carotene Selenium Glutathione Glutathione peroxidase activity	↓	Ogilvie et al. 1995 Goode et al 1995 Cowley et al 1996 Lyons et al 2001
<b>Burns</b>	Vit E β-carotene Vit C Selenium Zinc	↓	Berger et al. 1992 Gosling et al. 1995 Rock et al. 1997
<b>SIRS</b>	Vit E β-carotene Selenium	↓	Hawker et al. 1990 Forcevill et al. 1991 Curran et al. 2000
<b>Trauma</b>	Vit E β-carotene Selenium Zinc	↓	Berger et al. 1992 Young et al. 1998 Weiss et al. 1998
<b>Acute Renal Failure</b>	Selenium	↓	Makropoulos et al. 1997
<b>Mixed ICU</b>	Vit E Vit C	↓	Takedo et al. 1984 Schorah et al. 1996 Barelli et al. 1996 Kharb et al. 1999

**1.5.5.1 What doses of antioxidants supplementation are safe in critically ill patients?**

In 2000, the US Food and Nutrition Board of the Institute of Medicine defined and then revised (in 2002), tolerable upper intake levels (UL) of antioxidant supplements, which are considered the highest daily nutrient intakes that are unlikely to pose a risk of adverse health effects for almost all individuals in the general population (Table 1.6).

The UL was based on a no-observed-adverse-effect level (NOAEL), which is the highest intake of a nutrient, at which no adverse effects have been observed, in humans. If no other unknown factors are present for a more sensitive group of persons, the UL has the same value as the NOAEL. This is the case for vitamin C and zinc (table 1.6).<sup>64</sup>

**Table 1.6 Tolerable upper intake levels (UL) and No observed adverse effect levels (NOAEL) of antioxidants .<sup>64</sup>**

Age (years)	Vit. E (g)	Vit. C (g)	Se (µg)	Zn (mg)	β-carotenoids (mg)
UL 9-13	0,6	1,2	280	23	no
14- 18	0,8	1,8	400	34	recommen-
≥ 18	1	2	400	40	dations
NOAEL (adults)	250 mg/kg b.w.	2	800	40	

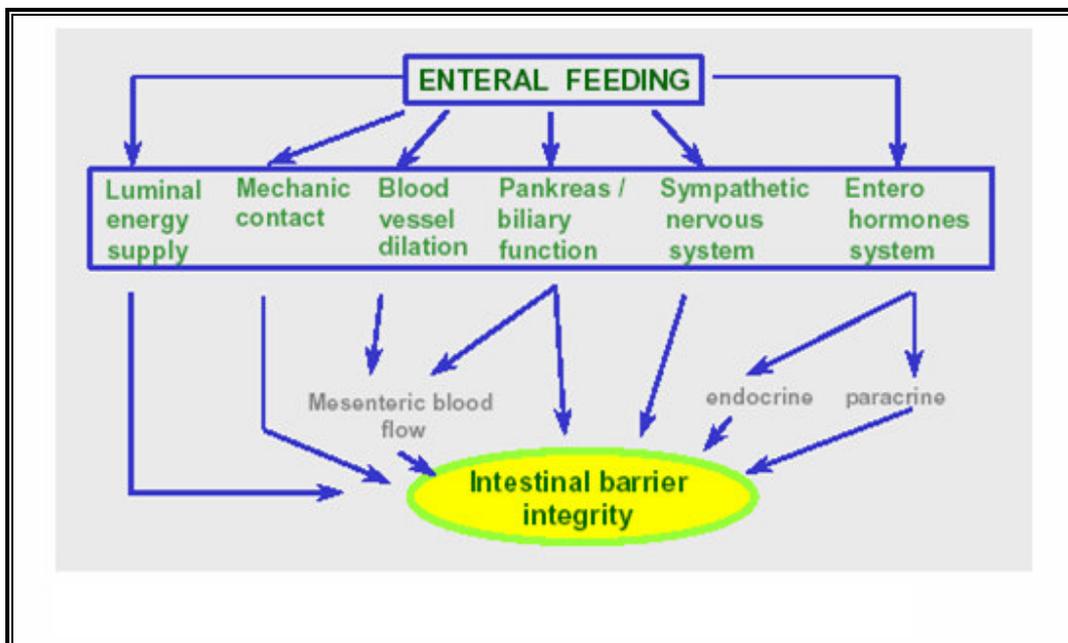
b.w. – body weight

## 1.6 EARLY ENTERAL NUTRITION IN THE CRITICALLY ILL

In the critically ill, nutritional support may be enteral or parenteral or a combination of the two. Parenteral administration may be a convenient approach in critically ill, ventilated patients, but it is recognised that enterally administered nutrition has additional advantages in preserving the gut in this patient population. Early enteral nutrition (EEN) seems to be a particularly important and most effective tool to maintain intestinal functions and reduce the risk of gut-derived infections. The term “use it or lose it” applies<sup>65</sup>. Despite some conflicting results, early enteral nutrition has been shown to reduce postoperative sepsis in surgical, trauma, and critically ill patients.<sup>66</sup> Therefore critically ill patients need very early luminal substrates in order to preserve gut structure and function. As we have already seen from the preceding discussion, gut dysfunction and

breakdown of the intestinal barrier may play a key role in the development of SIRS, sepsis and MOF, even if parenteral nutrition is chosen. The addition of early enteral feeding will ensure these added benefits.

The intestinal mucosa is unable to nourish itself completely from the blood. Approximately 50% of the enterocyte and 80% of the colonocyte nourishment depends on the luminal supply of nutrients. The lack of luminal substrates in starvation leads to atrophy and a rapid down regulation in size and function of the intestinal mucosa<sup>67</sup>. These morphological and functional changes are reversible by enteral, but not parenteral, feeding. This favourable effect of enteral nutrition is based on various factors (Figure 1.22).



**Figure 1.22 Enterotrophic effects of enteral nutrition**

The most essential benefits of enteral nutrition are the provision of nutrients and energy to the mucosal cells and the stimulation of epithelial cell metabolism by direct contact with luminal nutrients, i.e. the renewal of epithelial cells.<sup>65</sup>

Other effects of enteral nutrition, which help to maintain gut barrier integrity, are the increase in mucosal blood flow and improvement of intestinal perfusion,

stimulation of bile flow and pancreatic secretions as well as the release of enterotrophic gastrointestinal hormones such as gastrin and enteroglucagon.<sup>65</sup>

Most of the clinical studies, comparing total enteral versus total parenteral nutrition with respect to infectious outcome, have demonstrated the superiority of enteral nutrition.<sup>68 4</sup> When the goal is to support intestinal immunological and barrier function, an early start of EN seems to be of utmost importance.<sup>69 4</sup> The optimal time to start is, however, an unresolved issue.<sup>70</sup>

### **1.6.1 Optimum time for Initiation of Enteral feeding**

By definition “early enteral nutrition” starts within 24-72 hours after trauma or surgery. The immediate post-traumatic contact of the gut with nutrients will likely improve the situation in critical illness by several mechanisms.<sup>4</sup> EEN maintains or restores immune and gut barrier function.

The clinical consequences are: a better intestinal resorption capacity, improved substrate homeostasis and synthesis of visceral proteins, fewer complications and reduced gastrointestinal bleeding (Table 1.7).

Randomised trials demonstrated that enteral nutrition is associated with less mucosal permeability, enhanced wound healing, improved nutritional outcomes and lower costs. Small, unblinded studies showed a decrease in septic morbidity in enterally-fed abdominal trauma patients and patients with pancreatitis.<sup>10</sup>

**Table 1.7 Suggested benefits of early enteral nutrition in critically ill patients**

<ul style="list-style-type: none"> <li>• Intestinal barrier - <b>Protection</b> <ul style="list-style-type: none"> <li>- Bacterial translocation ↓</li> <li>- Septic morbidity ↓</li> <li>- Multiorgan dysfunction ↓</li> <li>- Infection rate ↓</li> </ul> </li> <li>• Stress response - <b>Attenuation</b> <ul style="list-style-type: none"> <li>- Stress hormone release ↓</li> <li>- Mediator release ↓</li> <li>- Energy expenditure ↓</li> <li>- Catabolism ↓</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Substrate utilization - <b>Improvement</b> <ul style="list-style-type: none"> <li>- Substrate homeostasis ↑</li> <li>- Visceral protein synthesis ↑</li> <li>- Nutritional assessment ↑</li> </ul> </li> <li>• Substrate tolerance - <b>Improvement</b> <ul style="list-style-type: none"> <li>- Visceral organ integrity ↑</li> <li>- Intestinal resorption capacity ↑</li> <li>- Gastrointestinal bleeding ↓</li> </ul> </li> </ul>
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Clinical studies in critically ill patients support the hypothesis that very early enteral nutrition, that starts within 4-12 hrs after trauma, significantly improves the clinical outcome of patients: Chiarelli et al, were the first who confirmed the experimental results in burn patients (n=20). EEN was initiated 4-5 hours after admission in the intervention group and in the control group after 55-60 hours. The very early fed patients had a lower incidence of positive blood cultures (5 in 3 patients versus 33 in 7 control patients). It was not stated if the positive blood cultures were correlated with intestinal permeability.<sup>4 14 71</sup>

It is therefore recommended that enteral nutrition should start within the first hours during stress metabolism after trauma, and as soon as the macrohaemodynamic situation is stabilised, before breakdown of gut barrier and immune dysfunction occurs in critically ill patients. Using an evidence-based approach, the recommendation for EEN in critically ill patients is a Level I recommendation.<sup>69 72 73</sup>

Suchner et al<sup>4</sup> concluded that in practice, initiating early enteral nutrition in critically ill patients represents a necessity often not realized. But there is already

some clinical data that suggest that very early EN is possible, well tolerated and safe even in the most severely ill. If clinically prioritised, the barriers to EEN can often be overcome. Braga et al<sup>74</sup> evaluated the safety and tolerance of EEN after major digestive surgery for cancer in 650 patients. EEN was started within 12 hours via a naso-jejunal feeding tube or a jejunostomy. Gastrointestinal side effects of the EEN were observed in 30% of the patients. Abdominal cramps and bloating were the most frequent symptoms, while diarrhoea and vomiting occurred less frequently. Most of these side effects were successfully handled by reduction or temporary interruption of feeding, or by drugs. Only 59 (8.9%) of the patients had to be switched to PN because of refractory intolerance to EN. EEN-related mortality was 0.1% (1/650). The authors concluded that “the use of the gut early after surgery is safe and well tolerated” and should be the “first choice for nutritional support in this type of patient”.<sup>74</sup>

Despite this, there are often contraindications to enteral feeding in this patient group as they may not be easy to stabilise haemodynamically during this period. While moving in and out of the ebb phase of stress metabolism, they may be enterally intolerant with ileus and risk of aspiration, particularly to full volume feeds. It remains a challenge to achieve enteral-feeding benefits in these patients.

The ESPEN guidelines on enteral nutrition, published in January 2006, concluded that no data showed more improvement in relevant outcome parameters where early enteral nutrition was used in critically ill patients. However, the expert committee recommended early enteral feeding (<24h), for haemodynamically stable critically ill patients with a functioning gastrointestinal tract. No general amount could be given, and the committee recommended that nutritional therapy has to be adjusted to the progression/course of the disease and taking the gut tolerance into account. If the goal of 20-25ckal/kg BW/day enteral nutrition is not met within the first 3 days, then supplementary parenteral nutrition should be given.<sup>75</sup>

The aim should be to start EEN within 6 hours after trauma or surgery and as soon as the macrohaemodynamic situation is stabilized<sup>105 4</sup>

### **1.6.2. Optimum Constituents of Enteral Feeds in Early Enteral Feeding**

It seems that nutritionally complete enteral feed is not possible in severe stress metabolism because of malabsorption due to structural and functional impairments following mucosal injury. Practicability and efficacy of EEN are dependent on the pre-existing extent of the mucosal trauma (ischemic mucosal damage and mucosal atrophy) and the current degree of intestinal hypoperfusion. Absorption and utilization of nutrients is diminished, but the digestive capacity can adapt if luminal substrates are supplied.<sup>4 14 37</sup>

Enteral nutrition exerts its beneficial effects on gastrointestinal functions even if it does not constitute the total nutrient need. In patients being fed parenterally, the supplementary provision of even small amounts of luminal nutrients can help to maintain gut barrier function. Between 10% and 25% of total requirements provided by the enteral route seem to be sufficient to support the mucosal integrity and decrease the intestinal permeability.<sup>76 77</sup>

From the literature there are recommendations to start “minimal” EEN with 5-10ml of an elemental feed/hour. The feed should be fibre free with a caloric density of 1 kcal/ml. Additionally the requirements of energy, protein and other essential nutrients can be met parenterally.<sup>4 37</sup>

Because the goal of nutritional support has to focus on the preservation of organ function during severe stress metabolism<sup>4 37</sup>, it can be hypothesised that a special enteral feed for the gut (which contains the preferred substrates for the intestinal mucosa, glutamine and butyrate, as well as high antioxidants to compensate oxidative stress) will be of much more benefit to the patient than common elemental diets.

The field of nutritional support therapy has undergone a transformation since its conception. Originally artificial feeding was recommended as a means of providing energy, proteins, and essential micronutrients to offset muscle wasting and prevent starvation-induced immune depletion. Subsequently various dietary components have been used in an attempt to modulate immune function. Specific amino acids, long chain fatty acids and nucleic acids have been studied. Although the composition of nutrition therapy can influence host defense, the published literature is divided on the effectiveness of manipulating nutritional support formulas to achieve hard clinical endpoints.<sup>3 78</sup>

### **1.6.3 Jejunal vs Gastric Enteral Feeding**

It is now recognised that small bowel function and the ability to absorb nutrients remain intact despite critical illness, the presence of gastroparesis, and absent bowel sounds. In patients unable to tolerate gastric feeding, jejunal feeding may still be feasible, allowing the benefits of EEN even in the presence of contraindications to gastric feeding.<sup>37</sup>

Close monitoring of the patients is very important, because even minimal EN is an invasive therapeutic procedure, with the potential risk of gastric colonisation, aspiration, obstruction, feeding tube related complications, reflux and diarrhoea. The jejunal route of administration may overcome most of these problems.<sup>4 79 80</sup>

### **1.6.4 Volume of Enteral Feeds in Critically ill Patients**

Tolerance of enteral feeding is probably the most commonly used indicator in the clinical setting for monitoring the gut function in critically ill patients.

Clinical signs of enteral intolerance are gastric reflux, aspiration, delayed bowel movement, abdominal distension, diarrhoea and vomiting (Table 1.8). These signs reflect multiple gastrointestinal disorders such as mucosal injury following ischemia and reperfusion, bacterial overgrowth, motility disorders and reduced pancreatic functions.

**Table 1.8 Reasons for and consequences of limited enteral volume in the critically ill <sup>14</sup>**

Deranged motility	→	*gastric reflux
Reduced exocrine pancreatic functions		* aspiration * nausea, vomiting
Intestinal hypoperfusion and ischemic mucosal damage	→	* abdominal distentions and cramps * malabsorption * etc

Most critically ill patients do not reach their goal for prescribed enteral nutrition. Only 50-75% of the daily dosages are tolerated using standard enteral feed preparations. <sup>81 82</sup>

There is an interrelation between enteral volume tolerance and clinical outcome in critically ill patients. The patients with gastrointestinal complications in the study of Montejo et al <sup>83</sup> who received lower feeding volumes, stayed about 5 days longer in the hospital and had a significantly higher mortality (31% vs. 16%) than the patients without complications. Thus, a limited enteral volume tolerance can be a prognostic indicator of the severity of the illness and the clinical outcome. <sup>83</sup>

Furthermore, a limited enteral volume tolerance means a limited uptake of key nutrients for the gut and immune system which decreases the benefits of EEN. A limited enteral volume tolerance can directly influence the outcome of critically ill patients. Atkinson et al <sup>84</sup> verified that immune-enhancing diets can only improve the outcome of critically ill patients, if they receive and tolerate a certain amount of the enteral formula i.e. a certain amount of immunonutrients, which in this study translated into > 2500 ml of Impact (formula) within 72 hours of ICU admission.

Thus, with the currently available standard enteral feed preparations, the limited enteral volume tolerance prevents an efficient supply of key nutrients which are needed for the benefits of EEN in critical illness.

This indicates the need for new feeds which provide the necessary quantities of key nutrients in a lower volume. The Fresenius product Intestamin® has been developed to address this need, amongst others, and is the first commercially available feed of this kind available in South Africa.

## **1.7 IMMUNONUTRITION**

Over the past decade there has been increasing interest in using specific nutrients to modulate the immune system and improve host defense mechanisms.

Clinical trials suggested several benefits of immune-enhancing diets, including a reduction in infectious complications, ventilator days, and length of ICU and hospital stay.<sup>5 85 86</sup>

Improvements in clinical outcome with immunonutrition have generally been reported in surgical patients, which cannot easily be extrapolated to other patient populations.<sup>4 87</sup>

Guidelines for the use of immunonutrition, after analyzing the literature, are summarized in the table below.

**Table 1.9 Guidelines for the use off Immune-enhancing diets**

<b>Patients who should receive early enteral nutrition with immuneenhancing diet (IHD)</b>	
<b>Elective GI surgery</b>	<ul style="list-style-type: none"> <li>▪ moderate / severely malnourished patients (albumin &lt; 3.5g/dL) undergoing elective esophageal, gastric, pancreatic, or hepatobiliary surgery</li> <li>▪ more severely malnourished patients would likely benefit the most</li> <li>▪ severely malnourished patients with albumin &lt;2.8g/dL undergoing colonic and rectal surgery</li> </ul>
<b>Blunt and penetrating torso trauma</b>	<ul style="list-style-type: none"> <li>▪ Patients with ISS &gt; 18; score correlates with injuries to two or more body systems with a severe injury in at least one site</li> <li>▪ Patients with ATI &gt; 20; score correlates with severe injuries to the colon, pancreas, liver, duodenum, and/or stomach</li> </ul>
<b>Patients who may benefit from IED , but data are limited. (elective surgery)</b>	<ul style="list-style-type: none"> <li>▪ Patients undergoing aortic reconstruction with known chronic obstructive pulmonary disease.</li> <li>▪ Patients with pre-existing malnutrition undergoing major head and neck surgery.</li> <li>▪ Patients with third -degree burns &gt; 30% total body surface area burn.</li> <li>▪ Patients who are ventilator dependent, nonseptic, medical and surgical patients at risk of subsequent infectious morbidity.</li> </ul>
<b>Patients in whom early enteral feeding or IED s are inappropriate</b>	<ul style="list-style-type: none"> <li>▪ Admitted to the ICU for monitoring only.</li> <li>▪ Expected to resume an oral diet within 5 days</li> <li>▪ Have a bowel obstruction distal to the site of access for enteral feeding.</li> <li>▪ Have major upper GI hemorrhage caused by varices or peptic ulcer disease.</li> <li>▪ Are incompletely resuscitated with poor splanchnic perfusion.</li> </ul>

IED - Immune-enhancing diet

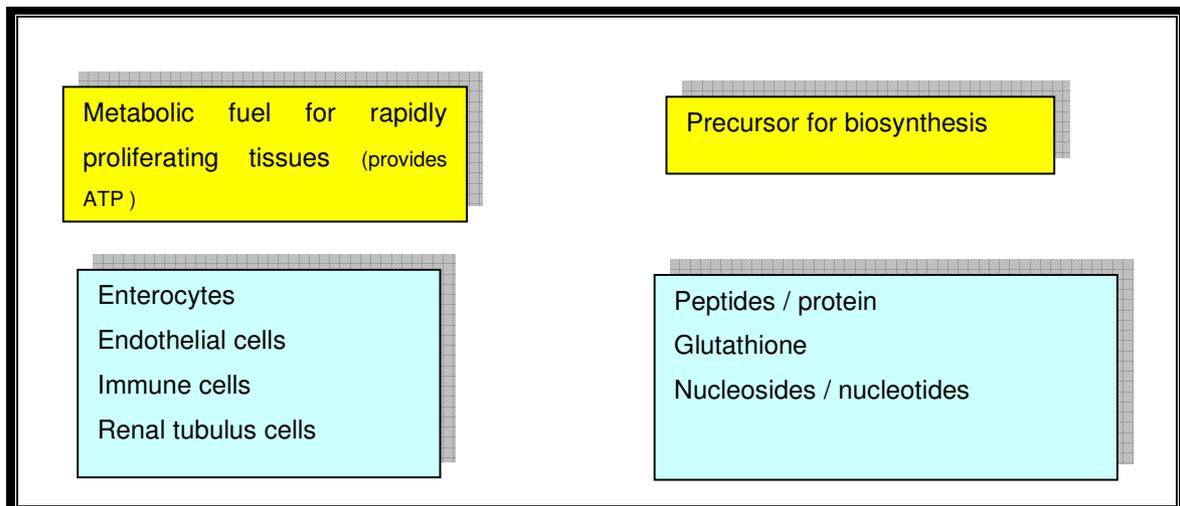
GI - Gastro-intestinal

## 1.7.1 Dietary Components with Immune-modulating effects

### 1.7.1.1 Glutamine

Glutamine is the most prevalent free amino acid in the human body. In skeletal muscle, glutamine constitutes > 60% of the total free amino acid pool. Glutamine was classified as a non-essential amino acid when it was demonstrated that it could be synthesized in the body, predominantly in the skeletal muscle. However glutamine should be reclassified as a conditionally essential amino acid in the catabolic state, because the body's glutamine expenditure exceeds synthesis and low glutamine levels in plasma are associated with poor clinical outcome.<sup>14 88</sup>

In normal metabolism, glutamine synthesis and expenditure are well balanced. Consequently, a state of deficiency does not exist and the amino acid may fulfill its important functions. The main functions of glutamine are illustrated in Figure 1.23 and include two main areas, namely metabolic fuel for rapidly proliferating tissues such as the enterocytes, endothelial cells, immune cells and the renal tubular cells, and a precursor for biosynthesis of peptides (protein), glutathione and nucleotides.



**Figure 1.23 Metabolic functions of glutamine**

(Source: Martindale RG, Sawai R. 2007<sup>14</sup>)

However, one of the immediate responses to trauma or surgical stress and, in particular to corticosteroids, is the increased export of glutamine from the free amino acid pool in muscle to the intestine and immune system.<sup>14</sup>

Glutamine is therefore required in increased amounts to manifest optimal tissue responses to catabolism, inflammation and infections, and endogenous synthesis cannot keep pace with increased demands in these conditions. In the catabolic state, the provision of conditionally essential glutamine should be considered a necessary replacement of deficiency rather than a supplementation<sup>89</sup>.

The frequently high requirements of glutamine in critically ill patients cannot be met with the available enteral immunonutrition formulas, even when the patients tolerate the full recommended dosage of 1.5-2 l/day.

It is recommended that a postoperative patient receive about 1,5 g protein/kg body weight per day. The usual glutamine dose in this individual should be about 0,3 g/kg body weight per day. For a 60-70kg patient this provides about 20g glutamine/d. A severely injured patient with multiple trauma represents a more severe state of stress. Such a patient would therefore require more glutamine, up to 30 g/d.<sup>90</sup>

To achieve such a high glutamine supply with currently available ready-to-use tube feeds, would imply an intake up to 2,5-3 litres per day, as immunonutrition diets roughly contain 1g glutamine/100ml as part of a whole protein source. Such a high volume will definitely not be tolerated by critically ill patients within the first days of enteral feeding.

An innovative approach using glutamine containing dipeptides in enteral nutrition facilitates high dosage glutamine therapy with ready-to-use tube feedings within a low volume for the first time

It seems logical that considerations should be given to giving glutamine very early on in the course of a critical illness, to remedy firstly any immune system dysfunction and secondly to prevent any further deactivation of the immune system. This approach has already shown promising results in randomised clinical studies. In one randomised controlled study, glutamine supplemental enteral nutrition (up to 30 g/d) was commenced within 48 hours of trauma via a nasoduodenal tube for a minimum of 5 days. There was a significant reduction in the 15 day incidence of pneumonia, bacteraemia and severe sepsis. Measurement of the soluble TNF (Tumour Necrosis Factor) receptors, as a marker of a systemic inflammatory response, demonstrated that patients with glutamine supplementation had a lower systemic inflammatory response than control patients. In another study, early enteral glutamine supplemental feeding was commenced in multi-trauma critically ill patients within 48 hours. Rapid increase in feed volume via a naso-jejunal tube, such that by the 3<sup>rd</sup>-4<sup>th</sup> day they received between 25-30g glutamine/day. There was no overall survival difference but significant reduction in infectious morbidity in the first 15 days.<sup>89</sup>

In both groups mean plasma glutamine concentrations were below the lower limit of a reference range on day one. Compared with the control group, significantly higher concentrations of glutamine were seen on day 3, 4 and 5 in the glutamine group. Hence these studies showed that glutamine-enriched enteral nutrition can increase plasma glutamine concentrations in critically injured patients and improve patients' outcome. Jones et al conducted a randomised double-blind study in a more heterogeneous group of adult patients in the intensive care unit. Some patients were already infected, but able to tolerate enteral feeding.

The supply of 18g/d glutamine to these patients resulted in significantly reduced post-intervention hospital cost. They conclude that in critically ill patients in the intensive care unit, enteral feeds containing glutamine result in significant hospital cost benefits<sup>91 92</sup>.

Three sites of action may be considered, representing potential targets for glutamine:

- Mucosal barrier function
- Cellular defense function
- Local or systemic inflammatory response

### **Mucosal barrier**

Glutamine is a major source of energy for the rapidly dividing cells of the gastrointestinal tract (enterocytes, colonocytes) and the GALT represents an essential substance for maintenance of gut metabolism, structure and function. <sup>9 14</sup>

Sufficient availability of suitable substrates e.g. glutamine as well as early enteral nutrition are currently considered the major tools in maintaining the structure and functionality of the mucosal barrier. <sup>4 14</sup>

### **Cellular defense**

The nitrogen component of glutamine appears to play an important role in the maintenance of gut structure and function. It is a major component for the biosynthesis of nucleotides (playing a major role in proliferation) and amino sugars (playing a major role in lining of the gastrointestinal tract).

### **Inflammatory response**

In addition, glutamine-mediated glutathione synthesis is probably one of the most important factors when considering treatment for the systemic inflammatory response. It is proposed that glutathione synthesis is a crucial factor in the reversal of the clinical and biochemical signs of critical illness. <sup>4 14</sup>

### **1.7.1.2 Arginine**

Suchner et al hypothesised that specific immune-enhancing nutrients, especially arginine, may unfavourably intensify systemic inflammation and consequently worsen the outcome in critically ill patients, because of its proinflammatory effects.<sup>93</sup>

The supplementation of arginine (like the other key nutrients for immunonutrition) is based on the observation that these nutrients become depleted in critical illness due to extensive consumption. But it might be possible that the availability of arginine in critical conditions needs to be lower than normal in order to avoid harmful effects in certain circumstances. Thus, not all substrates need to be replenished, because adequate levels have to be defined in accordance with the underlying pathophysiology.<sup>93</sup>

Moreover, arginine has been insufficiently investigated compared to other immunonutrients such as glutamine.

### **1.7.1.3 Short chain fatty acids (SCFA)**

The SCFA butyrate is a key substrate for intestinal nutrition, maintenance of mucosal integrity and restoration. Mechanisms by which SCFA may mediate intestinal proliferation and function include stimulation of local blood flow, production of exocrine pancreatic secretions, stimulation of the autonomic nervous system, and production of enterotrophic hormones.<sup>7 14 37</sup>

Usually butyrate is produced from dietary fibre in the large intestine (colon). However the supply of dietary fibre can be linked with some unwanted effects (such as abdominal distension, bacterial overgrowth and the risk of intestinal obstructions) in critically ill patients. Dietary fibre is thus contra-indicated in critically ill patients.

An alternative to the enteral fibre supply can be the supplementation with SCFA. Several experimental and clinical studies have shown beneficial effects of orally/enterally and parenterally administered SCFA. For example, SCFA stimulated intestinal mucosa proliferation, reduced small bowel atrophy during TPN and enhanced intestinal adaptation after bowel surgery .<sup>94</sup>

It could therefore be stated that SCFA are essential to support the gut barrier in critical illness because of their importance as main fuels for the intestinal mucosa.<sup>95</sup>

Intravenous infusion of SCFA (sodium butyrate, acetate and propionate) significantly reduced small bowel atrophy, which was caused by starvation of the gut, during parenteral feeding of rats.

Because of the above-mentioned benefits of butyrate, this nutrient is important in the support of the gut in critically ill patients. It is postulated from *in vitro* results that for the stimulation of intestinal cell proliferation and the maintenance of mucosal integrity, a dosage of 10-20 mmol butyrate will be effective. This dose reflects the minimum of the normal daily butyrate production from undigested carbohydrates in the large intestine which is about 10-60 mmol.

### **1.7.2 Intestamin**

Intestamin® is a small volume enteral immunonutritional supplement which provides supplementation of parenteral feeds with small volumes of 500ml per day (24 hours), which is a lower volume and therefore better tolerated than standard enteral feeds for similar essential enteral supplementation.

Semi-elemental substrates in the form of glutamine dipeptides, glycine and tributyrine provide energy substrates even in the absence of functional digestive processes. Intestamin® offers a new source of one of the most important intestinal fuels, the SCFA butyrate – in form of the structured lipid “Tributylin”.

Tributylin (1,2,3-Tributyrylglycerol= C<sub>15</sub>H<sub>26</sub>O<sub>6</sub>) is a structured lipid consisting of three molecules of butyrate esterified with glycerol. Both components of tributyrin, butyrate and glycerol, are normal intermediate products in human metabolism. Besides the supply in milk fat, butyrate is produced by microbial fermentation of dietary fibre in the large intestine. Glycerol is an intermediate substance in fat metabolism which is produced during normal digestion. Industrially produced tributyrin is used as a “naturally identical flavouring food additive” in baked goods, beverages, fats and oils, dairy desserts and other foods.

For these purposes tributyrin is “generally recognised as safe” (GRAS) by the US Food and Drug Administration (FDA: 21CFR184.1903).

Selective antioxidant additives include glutamine, antioxidant vitamins, selenium and zinc. Research has postulated that the dose and combination of additives chosen for Intestamin® have an advantage over other standard feeds, as a greater concentration is available in a smaller volume for enhanced absorption and tolerance.

Arginine has been omitted based on the studies which have suggested that it may worsen the outcome.<sup>14 20 21 37 101</sup>

Intestamin® (manufactured by Fresenius Kabi, Bad Homburg, Germany) content per 500ml contains:

- 259k cal
- 1g tributyrin (as a substitute for fiber)
- 30g glutamine
- 300g selenium
- 20mg zinc
- 1500mg vitamin C
- 500mg vitamin E
- 10mg carotene

The manufacturer's recommendation for the use of Intestamin® is as an enteral supplement in combination with parenteral and/or enteral nutrition, as it contains antioxidant vitamins, and trace elements, glutamine, and SCFAs.

## **1.8 MOTIVATION FOR THE STUDY**

Studies evaluating immune-modulating diets (IMD) have suggested that they are associated with a number of beneficial effects, including a reduction in infectious complications, fewer days on antibiotics and ventilator, and shorter ICU and hospital stay. These effects, in turn, have been shown to be associated with cost benefits. There has been concern, however, that better outcome is observed only in patients who tolerate significant amounts of enteral nutrition. Thus, the claimed benefit cannot be extrapolated to all patients. In fact, critically ill patients with severe sepsis, shock and organ failure not only do not benefit, but may actually be harmed by treatment with IMD, since current immunonutrient supplemental products are unsuitable for this type of patient.<sup>96 79</sup> Major problems arising from current IMD are: inadequate provision of 'key nutrients' via the enteral route due to feeding intolerance, lack of short chain fatty acids due to reduced enteral tolerance of fiber, insufficient capacity to counteract free radical induced damage of the intestinal barrier, administration of pro-inflammatory and free radical generating substrates.

Research has been directed at finding the optimum nutritional composition, timing and route to support the very important immune and barrier functions of the gastrointestinal tract in critically ill patients. It can be hypothesised that certain substrates added to standard enteral feeds can modulate the immune response and may decrease infectious morbidity in these patients, and that the introduction of early enteral feeding has significant benefits on maintenance of gut integrity.

Bearing this in mind, what would constitute the ideal early enteral feed in these patients and how does this translate into a choice between enteral feeds?

As digestive processes can be assumed to be partially or entirely dysfunctional in critical illness, a supplemental enteral feed, aiming to provide caloric support, must do so in a form which is easily absorbable despite gut dysfunction. Semi-elemental feeds would be expected to be better tolerated and more easily absorbed.

Currently available immunonutrition formulas provide effective dosages of key nutrients in daily volumes of 1500-2000 ml. The common dosage scheme recommends 20-25 ml/h to start with, which amounts to a total of about 500 ml on the first postoperative/post-traumatic day. The feeding volume is then increased stepwise to approximately 750 ml on the 2<sup>nd</sup> day, 1000 ml on the 3<sup>rd</sup> day and further, to the complete daily dosage of 1500 ml on the 4<sup>th</sup> or 5<sup>th</sup> day.<sup>97</sup>

However, there are many critically ill patients who do not tolerate a daily dosage of 1500 ml of an enteral feed on the 4<sup>th</sup> or 5<sup>th</sup> postoperative day. Especially the most severely ill patients, frequently suffer from intolerance to enteral feeding. Some of these patients tolerate only very small amounts of an enteral feed, others do not tolerate enteral feeding at all.

Ideally the enteral feed chosen for these patients should include the caloric requirements in the smallest possible volume for maximum tolerance.

From the previous discussions, we can conclude that certain supplements will be advantageous for a positive effect on the stress cycle. Antioxidants and immunoactive substrates like glutamine have been shown to have the potential for additional benefit, and therefore selective enrichment with these substances may result in further potential benefits.

With the above points in mind, Intestamin® has been formulated as a unique new enteral supplement which may be considered one of the second generation enteral supplemental feeds and could be associated with improved outcomes in critically ill patients.

This study was undertaken to test this hypothesis by using selected infection markers, duration of ventilation and ICU stay as surrogate markers for outcome in a population of critically ill patients.

## **CHAPTER 2 : METHODOLOGY**

## **2.1 STUDY AIM**

The aim of the study was to investigate the effect of Intestamin® administration to critically ill patients on the prevalence of infection, ventilation requirements and duration of Intensive Care Unit (ICU) stay.

## **2.2 OBJECTIVES**

The primary objectives were to:

- determine if Intestamin® administration decreases infection rate in the critically ill patient,
- determine if Intestamin® administration decreases ventilation days in the critically ill patient,
- determine if Intestamin® administration decreases the length of stay in the ICU for the critically ill patient.

A secondary objective was to assess the tolerability of early enteral nutrition supplementation with Intestamin® in critically ill patients.

## **2.3 HYPOTHESIS**

Intestamin® administered to the critically ill patient has beneficial effects on the prevalence of nosocomial infection rates, ventilation requirements and duration of stay in the ICU.

## **2.4 STUDY DESIGN AND STUDY POPULATION**

The study design was an open label, retrospective, case control, analytical study, of patients admitted to the adult general ICU of Netcare The Bay Hospital, Richards Bay, Kwazulu Natal, between June 2003 and November 2003, who were treated with Intestamin® supplementation, in addition to the normal nutrition support, according to standard practice protocols. Data from the patients who met the inclusion criteria for the study was collected on a daily basis by the

researcher. Matched case controls were evaluated from the files of patients who were admitted to the same ICU between January 2002 until end of May 2003, but who were not treated with Intestamin®.

The data from the matched case controls was collected from the clinical records and laboratory records of demographically matched patients with similar conditions to the intervention group. The control group were matched with the intervention group, making use of the APACHE 2 scoring system.<sup>60</sup> These two groups were considered comparable as there were no protocol changes in the ICU management in this unit during the stated periods and the management was directed by the same senior clinicians. The diagnostic criteria and treatment procedures would therefore be expected to stay the same, except for the use of Intestamin® in the intervention group.

The Bay Hospital ICU is a nine bed unit fully equipped to deal with medical, surgical and trauma patients in need of intensive care treatment. Each patient has a dedicated registered nurse, who is responsible for all the nursing needs of the patient, continuous monitoring and observations and collection of laboratory samples. Physiotherapy by registered physiotherapists occurs twice daily for chest physiotherapy and the collection of sputum aspirate samples, as requested by the overseeing physician.

## **2.5 PATIENT SELECTION**

Patients were selected for the study from post-surgery and post-trauma patients at high risk of SIRS and severe sepsis and critically ill patients with established SIRS or severe sepsis. This included patients following major surgery, severe burns, severe head injury, severe blunt or penetrating torso trauma and acute pancreatitis.

Patients were excluded from the study if enteral feeding was medically contraindicated. This included patients with obstructive ileus, major upper GI

haemorrhage, caused by varices or peptic ulcer disease with a visible vessel on endoscopy, patients with impaired swallowing reflex, severe acute necrotising pancreatitis, metabolic coma (e.g diabetic, hepatic coma), uncompensated circulatory shock (ebb phase of stress metabolism), intractable diarrhoea (> 1500 ml watery stools/day), intestinal fistula (> 500ml output/day), small bowel necrosis following intestinal hypoperfusion and acute colonic pseudo-obstruction.

### **2.5.1 Inclusion criteria:**

- ICU admission
- Male and female patients
- Age 18-75 years
- High probability of developing SIRS or signs of SIRS as indicated by an APACHE II score of > 18
- Expected mortality of < 70% as indicated by APACHE II score of < 31
- Patients on mechanical ventilation

### **2.5.2 Exclusion criteria:**

- Age < 18 or > 75
- APACHE II score < 18
- APACHE II score > 31
- Patients not mechanically ventilated
- Patients in whom enteral feeding was medically contraindicated

The APACHE II score (Addendum A) is a general measure of disease severity based on physiological measurements, age and previous health condition. It is used in clinical research to stratify patients according to the severity of the disease in critical illness. This score was used to match patients in the control and intervention groups according to disease severity.<sup>60</sup>

The sample size of 12 patients in the intervention group was determined by the preset time lines of the study - of 6 months - for recruitment. During this period only 12 suitable patients met the inclusion criteria for the active arm of the study

from a total of 60 screened and these were then matched demographically and for disease severity with 12 retrospective controls. As a result of the small sample size, and bearing in mind that trials of enteral nutrition in this patient population usually need large numbers for statistical significance, it was recognised at this point that the trial would have to be considered as a pilot study on the subject, and would be unlikely to be definitive in its findings.

## **2.6 PATIENT NUTRITION SUPPORT**

### **2.6.1 Nutrition Support Regime**

Patients included in the intervention group received Intestamin® supplementation within 24 hours after enrollment in the trial, at 10ml/hr, increasing the rate by 10ml/hr every four hours to reach a target of 500ml/day within 48 hours. After four hours of supplemental feeding, the feed was stopped for one hour, nasogastric aspirate was done by the registered nurse looking after the patient and a supplement feeding protocol was followed. The protocol required that when nasogastric aspirate was less than 50% of the total amount of supplemental feed fed, the supplemental feed (Intestamin®) would be increased by 50% of the current running rate. The Intestamin® was given to the intervention group for a five day period. Complete enteral formulas (disease-specific) were introduced from day 2, together with Intestamin®, at a running rate of 35ml/hr and the same feeding protocol was followed to increase the running rate of the complete enteral formulas. Following the ICU's feeding regime, nutritional needs for each patient were calculated individually to supply 25kcal/kg. All enteral feeds were given via the nasojejunal route. When any feeding intolerance was encountered, the Intestamin® was not decreased or stopped, but the complete enteral feed was either changed to another feed or TPN was initiated.

Gastrointestinal tolerance was assessed daily in all patients by clinical examination. Signs considered indicative of gastrointestinal intolerance included:

1. Abdominal distention or bloating. If the abdomen was distended, but soft to palpation, a 48 hour waiting period was initiated with no change in the feeding but close monitoring. If abdominal distention persisted, and the patient was already on a standard enteral feed, it was changed to a semi-elemental feed together with Intestamin®. If symptoms persisted for another 48 hours, standard enteral feeding was stopped and TPN was commenced, but Intestamin® was still continued. Only if the intolerance continued or worsened in the 24 hours after changing to TPN, would the Intestamin then be stopped or temporarily interrupted.
2. Intractable diarrhoea. This was defined as more than 1500ml watery stools/day. If this was observed, standard enteral feeding was stopped and TPN was commenced. The Intestamin® was continued, and only if the diarrhoea persisted despite the change to TPN, would the Intestamin® be discontinued.
3. Gastroparesis. When nasogastric drainage was more than 500ml/24 hours only Intestamin® in combination with TPN was used until nasogastric drainage was less than 150ml/24hours, at which point standard enteral feeding was reintroduced.
4. Nausea and Vomiting. If the patient demonstrated nausea and vomiting, the running rate of the standard formula was decreased by half. The Intestamin® running rate was continued unchanged. If the symptoms were relieved within 24 hours, the standard formula was reintroduced at the previous running rate. If symptoms persisted, standard enteral feeding was stopped and TPN was commenced. The Intestamin® was continued, and only if the nausea and vomiting persisted despite the change to TPN, would the Intestamin® be discontinued.

## 2.7 DATA COLLECTION

Development of respiratory and urinary sepsis were used as surrogate markers for progression to severe sepsis and SIRS. Additionally, duration of ventilation and ICU stay were considered representative of the response to treatment and degree of clinical complications. The following information was collected for each patient studied:

1. At entry to the study and weekly: urine chemistry, microscopy and culture, sputum microscopy and culture, blood culture.
2. At entry to the study and daily according to standard ICU protocol: vital signs including temperature, heart rate, blood pressure, urine output, fluid intake, full blood count including serum haemoglobin and white cell count, urea and electrolytes, blood glucose.
3. At entry to study and weekly: Liver function tests including serum albumin, serum calcium, magnesium and phosphate, chest X-ray.
4. As indicated clinically (based on clinical suspicion of infection): urine catheter tip culture, sputum microscopy and culture, blood culture, central line tip culture, chest X-ray.

Where sputum could not be produced spontaneously or with physiotherapy assistance or in patients with tracheostomies, tracheal aspirate specimens were taken for microscopy and culture instead of sputum specimens.

All sputum specimens for culture were taken by the ICU trained nursing staff or physiotherapist using standard aseptic technique and protocols for this ICU.

All urine specimens for culture were taken after the catheter was clamped for 10 minutes by the ICU trained nursing staff using standard aseptic technique and protocols for this ICU.

All laboratory haematology blood microbiology and chemistry specimens were taken by the ICU trained nursing staff or laboratory phlebotomist using standard aseptic technique and protocols for this ICU and hospital.

Chest X Rays were performed by one of the radiographers of the private radiology practice of Drs Nisbet and Govender and reported by one of the specialist radiologists in the practice.

Clinical evaluations were performed by the specialist surgeon in charge of the case, Dr P van Rooyan or Dr G Kelling.

In addition, duration of ICU stay and duration of mechanical ventilation were calculated from the clinical records and ICU charts by the principal investigator with 1 day being from 06.00 to 05.59 the following day.

Blood, urine and sputum specimens were analyzed by an accredited private laboratory, Drs Bouwer & Partners, Richards Bay Laboratory, (Ampath National Laboratories facility, accreditation number: M0153; ISO accredited; ISO 15189:2003, expires May 2011) using standardized verified techniques performed by registered pathology technologists.

The blood samples were analysed using the ADVIA 120 Haematology system. For white blood count, the whole blood sample is mixed with ADVIA 120 BASO reagent that contains acid and surfactant. The red cells are haemolyzed, and the white blood cells are then analyzed using 2 angle scatter signals.

The Beckman SYNCHRON CX system was used to analyse the liver function tests by making use of an enzymatic rate method for each individual liver enzyme test.<sup>98</sup>

With the Beckman SYNCHRON CX system, Albumin Reagent is used to measure albumin concentration with a timed-endpoint method. In the reaction, albumin combines with bromocresol purple to form a colored product.<sup>98</sup>

Total Protein Reagent is used to measure the total protein concentration by a timed-endpoint biuret method. (Beckman SYNCHRON CX system).<sup>98</sup>

The Beckman SYNCHRON CX4 system was used to determine the measurements of sodium, potassium, chloride, carbon dioxide, glucose, urea nitrogen, creatinine and calcium in various serum specimens. Each test is performed using specific electrodes and individual chemistry reactions. The concentration signals originating at the electrodes in the flow cell, and the sensors in the reaction cups are converted by analog amplifiers to actual concentration values.<sup>98</sup>

Endotracheal and sputum specimens were cultured by inoculation using a sterile swab on Colombia blood agar plate (5% CO<sub>2</sub>) with Optochin disc in pool, Chocolate agar plate (5% CO<sub>2</sub>) or MacConkey plate (O<sub>2</sub>). Gram stain was applied. The laboratory reported on the Gram stain, microscopic morphology and the quantification of all bacteria seen in relationship to the cell types that were present.

Urine specimens were macroscopically examined before being processed for abnormal color and the presence of blood. Thereafter quantitative cultures were performed on the specimens, making use of Sheep blood agar plates, MacConkey agar plates, Mueller Hinton agar plates and to detect antimicrobial substances present, Antimicrobial Substance Plates, were used.

All patient data was collected by the principal investigator from the patient charts and transcribed to an Excel data sheet. This dataset was sent for statistical analysis to the statistician.

Quality control at Ampath Laboratory is done internally as well as externally. For liver function tests, Synchron Level 1,2 and 3 are run daily, for full blood count ACT5 Normal, Low and High are run daily. A day-to-day variation of < 7% being the highest variance for a given determination. The laboratory belongs to the THISTLE EQA program, which covers Haematology and Clinical Chemistry external quality control, and these samples are run monthly.

## **2.8 DATA ANALYSIS**

All the results were collected and entered in a dataset making use of Microsoft Excel® in consultation with the appointed statistician. All statistical analyses were performed with the help of a statistician, Prof DG Nel, appointed by the Faculty of Health Science, Stellenbosch University.

Summary statistics were used to describe the variables. Variables were presented graphically in the form of histograms or frequency tables to see the nature of the distribution of the particular variables and to be able to identify possible outliers. Medians or means were used as the measures of central location for ordinal and continuous responses, and standard deviations and quartiles as indicators of spread. The Means ( $\bar{x}$ ) and standard deviations (SD) were reported where necessary for continuous or ordinal response variables in the format:  $\bar{x}$  [SD]. Tables with many characteristics of the variables involved, namely the mean value, the median (50<sup>th</sup> percentile), the mode (value with the highest frequency), the quartiles, the maximum and minimum values, standard deviation, were included in the descriptive statistical methods where relevant.

Chi-Square and Fisher's exact test were used for comparison of nominal or frequency data between groups. All reported p-values less than 0.05 were considered as significant for all tests performed.

Repeated-measures analysis of variance was used to evaluate treatment-related effects over time. Descriptive statistics were given for the different groups

compared. The Mann-Whitney test was used, and where more than two groups were compared the Kruskal-Wallis test was used. Normal probability plots of the residuals were done to determine whether data was normally distributed.

## **2.9 ETHICAL CONSIDERATIONS**

The study was approved by the Committee for Human Research of the Faculty of Health Sciences, Stellenbosch University (N04/10/166) (Addendum C) and conducted according to ICH GCP guidelines (Guidance on Good Clinical Practice and regulations by International Conference on Harmonization). Permission to access retrospective clinical data for this pilot study was granted by the treating surgeon in charge of each case and by the Bay Hospital Manager, Mrs B Moore. (Addendum D)

Each enrolled patient's identification information was omitted from study-related material to ensure participant anonymity and confidentiality. Upon entering the study, each participant received a unique subject identification identity number, which was used on all study-related material and documentation.

The data collected was only used for this specific study, and was not shared for any other purposes or studies.

## **CHAPTER 3: RESULTS**

### **3.1 DESCRIPTION OF SAMPLE**

A total of 60 patients, admitted to The Bay Hospital ICU between June 2003 and November 2003, were screened retrospectively, of which 12 met the entry criteria and were included in the study. Twelve controls who also met the criteria were selected from hospital records after a review of archived patient files.

The patients were matched in the intervention group ( $N = 12$ ) and the control group ( $N= 12$ ), using the APACHE II score (Addendum A) and demographics of each patient .

All patients included in the intervention group received Intestamin® enteral supplementation during the course of the study period.

The two groups were demographically comparable with no statistically significant differences between age and sex distribution (Table 3.1). Ages ranged in the intervention group between 22-77 years of age with a mean of 45.75 [16.24] years and in the control group between 28-67 with a mean of 46.42 [12.72] years of age.

Elective post surgery and emergency post surgery patients were included in both groups with mean APACHE II scores of 24 (range 20-29) in the intervention group and 24 (range 18-30) in the control group (Table 3.1).

**Table 3.1 The sociodemographic characteristics of the patients included in the study**

Variable	Control Group (CG)		Intervention Group (SG)	
	Male	Female	Male	Female
Number (N)	9	3	8	4
Number per Group	12		12	
Age mean [SD]	45.67 [14.41]	48.67 [7.02]	45.13 [19.09]	47.00 [10.68]
Group Age Mean [SD]	46.42 [12.72]		45.75 [16.24]	
P - value	0.60			
APACHE score / Group	25.00 [5.89]	22.33 [9.45]	23.75 [19.09]	25.25 [6.4]
P - value	0.78			
Elective Postoperative Patient	6	3	5	3
Emergency Postoperative Patient	3	0	3	1

Mann-Whitney U test significant if  $p < 0.05$ .

[SD] = Standard Deviation

APACHE = Acute Physiological Assessment and Chronic Health Evaluation

### 3.2 PATIENT NUTRITION SUPPORT

Patients included in the intervention group received Intestamin® supplementation within 24 hours after enrollment in the trial at 10ml/hr, increasing the rate by 10ml/hr every four hours to reach a target of 500ml/day within 48 hours. On day one, the intervention group received between 105ml-483ml of the supplement (Intestamin®). From day two the intervention group received the planned 500ml/day. The supplement Intestamin® was given to the intervention group for a five day period. Complete enteral formulas (disease-specific) were introduced

from day 2, at a running rate of 35ml/hr, increasing the rate by the same protocol that was followed when increasing the running rate of the complete enteral formulas. Complete enteral formulas reached a mean volume of 840ml on day 2, increasing to between 960ml-1320ml/day for the remainder of the period while enteral nutrition was needed. All enteral feeds were given via the nasojejunal route, and continued for at least 10 days. When any feeding intolerance was encountered, the Intestamin was not decreased or stopped, but the complete enteral feed was either changed to another feed or TPN was initiated.

Only minor gastrointestinal intolerance was experienced in the form of diarrhoea , occurring in only one of the patients in the intervention group, however this was less than 1500ml per 24 hours and lasted for only one day and no patient had to discontinue Intestamin® enteral feeding during the study.

### **3.3 INFECTION INDICATORS**

#### **3.3.1 Respiratory Infections**

Five variables were collected in respect to respiratory infections: temperature spike and elevated white cell count, chest X-ray changes suggestive of infection, pus cells in the sputum or tracheal aspirate and positive culture in the sputum or tracheal aspirate.

For the purposes of this thesis:

***Suspected Respiratory Infection:*** was defined when two or more of the variables (Table 3.2) were positive. The temperature spike and elevated white cell count were only considered significant if they occurred with other signs or symptoms of respiratory disease as opposed to an alternative site of sepsis.

***Confirmed respiratory infection was defined*** when a positive culture was supported by one other variable.

**Tabel 3.2 Variables supportive of respiratory infection**

<b>Variable</b>	<b>Description</b>
<b>Temperature spike</b>	Temperature measure above 36.8°C
<b>Positive culture growth in tracheal aspirate</b>	Laboratory confirmed positive bacterial culture from tracheal aspirate sample
<b>Chest X-ray findings suggestive of infection</b>	Pulmonary infiltration opacification or consolidation as reported by a Radiologist
<b>Presence of pus cells in tracheal aspirate</b>	Pus cells seen on microscopy by the laboratory tracheal aspirate specimen
<b>Raised white blood count</b>	White blood count of greater than $10 \times 10^9/L$ , on peripheral blood sample as measured by the laboratory.

Categorical data analysis of the respiratory indicators of infection used for the purpose of this study, between the intervention and control group, was done using the Mann-Whitney U test.

This showed no statistically significant difference between intervention and control group for temperature spikes ( $p=0.54$ ), white blood count ( $p=0.95$ ) or chest x-ray findings ( $p=0.47$ ) (Table 3.3).

However, statistically significant differences were found between the two groups for the presence of pus cells ( $p=0.003$ ) and positive culture growth in the tracheal aspirate specimen ( $p=0.033$ ) (Table 3.3).

The intervention group showed a higher incidence of pus cells and the control group a higher incidence of culture growth.

**Table 3.3: Respiratory indicators of infection used in the study**

Group	Temperature spikes Mean [Standard Deviation]	Tracheal aspirate culture growth Mean [Standard Deviation]	Pus cells in traceal aspirate Mean [Standard Deviation]	Chest X-ray confirming a chest infection [Standard Deviation]	White Blood count total Mean [Standard Deviation]
<b>Control Group</b>	3.92 [1.62]	2.67 [4.85]	0.00 [0.00]	12,46 [5.73]	13.97 [5.61]
<b>Intervention Group</b>	5.33 [1.62]	0.00 [0.00]	2.50 [4.50]	14.32 [6,72]	14.32[1.65]
<b>p - level</b>	p = 0.54	<b>p = 0.033</b>	<b>p = 0.003</b>	p = 0.47	p =0.95

(Mann-Whitney U Test significant if  $p < 0.05$ )

A statistically significant difference was found between suspected and confirmed infections within the intervention group in favour of fewer confirmed respiratory infections ( $p=0.01$ ), but no statistically significant difference between suspected and confirmed infections in the control group ( $p=0.14$ ) (Table 3.4).

Overall, between the intervention and control groups, there was statistically fewer confirmed respiratory infections in the intervention group ( $p=0.05$ ) but no statistically significant difference between the two groups for suspected respiratory infections ( $p=0.2$ ). (Table 3.4)

**Table 3.4 Confirmed and suspected respiratory infection**

	Suspected Respiratory infections Mean [SD]	Confirmed Respiratory infections Mean [SD]	p-value within a group
<b>Intervention Group</b>	6.67 [8.08]	0.08 [0.28]	<b>0.01</b>
<b>Control Group</b>	3.33 [3.33]	1.58 [2.47]	0.14
<b>P-value between groups</b>	0.2	<b>0.05</b>	

ANOVA – test significant if  $p < 0.05$

### 3.3.2 Urinary Tract Infections

Five variables were collected in respect to urinary infections: temperature spike and elevated white cell count, presence of pus cells in the urine, positive urine culture and positive urinary catheter tip culture.

For the purposes of this thesis:

***Suspected urinary tract infection*** was the term used when two or more of the variables (Table 3.5) were positive. The temperature spike and elevated white cell count were only considered significant if they occurred with other signs or symptoms of urinary disease, as opposed to an alternative site of sepsis.

***Confirmed urinary tract infection*** was the term used when a positive culture was supported by one or more variables.

**Table 3.5: Variables supportive of urinary tract infection used in the study**

<b>Variable</b>	<b>Description</b>
<b>Temperature spike</b>	Temperature measured above 36.8°C
<b>Positive culture growth in urine catheter tip</b>	Laboratory confirmed positive bacterial culture from urine catheter tip sample
<b>Positive culture growth in urine</b>	Laboratory confirmed positive bacterial culture from urine sample
<b>Presence of pus cells in urine sample</b>	Pus cells seen on microscopy by the laboratory in the urine specimen
<b>Raised white blood count</b>	White blood count of greater than $10 \times 10^9/L$ , on peripheral blood sample as measured by the laboratory.

Categorical data analysis of the indicators of urinary tract infection used for the purpose of this study, between the intervention and control group, was done using the Mann-Whitney U test.

This showed no statistically significant differences between the intervention and control groups for temperature spikes ( $p=0.54$ ), urine culture ( $p=0.54$ ) and white blood cell count findings ( $p=0.95$ ) (Table 3.6).

Statistically significant differences were found between the two groups for pus cells ( $p=0.01$ ), more in the intervention group and positive culture growth from catheter tip samples ( $p=0.04$ ), less in the intervention group.

The intervention group had a higher frequency of pus cells in the urine and the control group a higher incidence of positive urine catheter tip culture (Table 3.6).

**Table 3.6: Urinary tract infection indicators**

Group	Temperature spikes Mean [Standard Deviation]	Urine Catheter culture growth total Mean [Standard Deviation]	Urine culture growth total Mean [Standard Deviation]	Pus Cells in urine samples Mean [Standard Deviation]	White Blood Count total Mean [Standard Deviation]
<b>Control Group</b>	3.92 (3.4)	3.00 (4.05)	3.92 (3.4)	2.05 (5.14)	13.97 (5.61)
<b>Intervention Group</b>	5.33 (7.16)	0.41 (0.79)	5.33 (7.16)	3.67 (4.75)	14.32 (1.65)
<b>p-level</b>	0.54	<b>0.04</b>	0.54	<b>0.01</b>	<b>0.95</b>

(Mann-Whitney U Test significant if  $p < 0.05$ )

Although there was a statistically significant difference between suspected and confirmed urinary tract infections within the intervention group ( $p=0.03$ ) in favour of fewer confirmed infections, there was no statistically significant differences in confirmed ( $p=0.08$ ) or suspected ( $p=0.34$ ) infections between the intervention and control groups (Table 3.7).

**Table 3.7 Confirmed and suspected urinary tract infections**

	Suspected urinary tract infections Mean [SD]	Confirmed urinary tract infections Mean [SD]	p-value within a group Mean [SD]
<b>Intervention Group</b>	5.25 [6.97]	0.66 [0.89]	<b>0.03</b>
<b>Control Group</b>	3.08 [3.23]	2.92 [4.10]	0.91
<b>P-value between groups</b>	0.34	0.08	

ANOVA test significant if  $p < 0.05$

### 3.3.3 Septicemia

Three variables were collected in support of a diagnosis of septicemia, i.e. temperature spike, raised white cell count and a positive blood culture. For the purposes of this study, septicemia was deemed to be present when a positive blood culture was supported by one other variable (Table 3.8).

**Table 3.8 Variables supportive of septicemia infection**

Variable	Description
Temperature spike	Temperature measure above 36.8°C
Positive culture growth in blood	Laboratory confirmed positive bacterial culture from blood sample
Raised white blood count	White blood count of greater than $10 \times 10^9/L$ , on peripheral blood sample as measured by the laboratory

Categorical data analysis between the intervention and control group, making use of the Mann-Whitney U test, did not differ significantly with respect to any of the variables (Table 3.9).

**Table 3.9 Sepsis indicators**

Group	Variables		
	Temperature Spikes Mean [SD]	White Blood Count total Mean [SD]	Blood Culture Growth Mean [SD]
Control Group	3.92 [3.4]	13.97[5.61]	0.25 [0.62]
Intervention Group	5.33 [7.16]	14.32[1.65]	2.83 [5.31]
p-value	0.54	0.95	0.11

Mann-Whitney U test significant if  $p < 0.05$

[SD: Standard deviation]

When data was analysed for those patients who were diagnosed with septicemia, no statistically significant differences were found within or between the intervention and control groups (Table 3.10).

**Table 3.10 Prevalence of confirmed and suspected septicemia**

	<b>Suspected Septicemia (Mean) [SD]</b>	<b>Confirmed Septicemia</b>	<b>p-value within a group</b>
<b>Intervention Group</b>	4.25 [5.08]	3.08 [4.14]	0,16
<b>Control Group</b>	3.25 [3.16]	1.17 [1.70]	0.06
<b>P-value between Groups</b>	0.57	0.15	

ANOVA test significant if  $p < 0.05$

When all the sepsis data was combined for confirmed infections, there was a borderline statistically significant difference between the intervention group and control groups for respiratory infections ( $p=0.05$ ), with more confirmed infections in the control group. There was no statistically significant difference between the groups for either urinary tract infections ( $p=0.08$ ) or septicemia ( $p=0.15$ ), nor was there a statistically significant difference between the two groups when all the data was combined ( $p=0.79$ ). (Table 3.11)

**Table 3.11 Combined data for confirmed infections**

	<b>Confirmed respiratory infection Mean [SD]</b>	<b>Confirmed urinary tract infection Mean [SD]</b>	<b>Septicemia Mean [SD]</b>	<b>Total</b>
<b>Intervention Group</b>	0.08 [0.28]	0.66 [0.89]	3.08 [4.14]	3.50 [4.76]
<b>Control Group</b>	1.58 [2.47]	2.92 [4.10]	1.17 [1.70]	4.08 [6.02]
<b>p- value</b>	0.05	0.08	0.15	0.79

ANOVA test significant if  $p < 0.05$

### 3.3.4 Ventilation days

For the purposes of this study, ventilation days were defined as total days a patient spent on a ventilator during the ICU stay. A day was defined as being from 06.00am to 05.59am or part thereof, and was taken from the ICU clinical chart on which all ventilation parameters were recorded hourly by the ICU nurse in charge of the patient. No significant difference was found between the intervention and control groups for number of days spent on a ventilator ( $p=0.78$ ). The intervention group spent a mean of 11.08 days and the control group a mean of 12.67 days on the ventilator (Table 3.12).

**Table 3.12: Ventilator Days**

<b>Group</b>	<b>Ventilator Days Total Mean</b>	<b>Ventilator Days Total SD</b>	<b>P-level (significant <math>p &lt; 0.05</math>)</b>
<b>Control Group</b>	<b>11.08</b>	<b>14.42</b>	<b>0.78 (not significant)</b>
<b>Intervention Group</b>	<b>12.67</b>	<b>13.17</b>	

**SD : Standard Deviation**

(Mann-Whitney U test,  $p = 0.78$ )

### 3.3.5 Length of Stay in the Intensive Care Unit

For the purpose of this study, length of stay in ICU was defined as from the day of admission to ICU as day one, and to the day of discharge from ICU as the last day in ICU. A day was defined as being from 06h00am until 05h59am, or any part thereof, and calculated from the ICU clinical chart. No significant differences were found between the intervention and control groups regarding days spent in the ICU. The intervention group spent a mean of 13.6 days and the control group spent a mean of 16.7 days in ICU. (Table 3.13, p=0.61)

**Table 3.13 : Days spent in Intensive Care Unit**

<b>Group</b>	<b>Days in ICU Total Mean</b>	<b>Days in ICU Total SD</b>	<b>P-level (significant p&lt;0.05)</b>
<b>Control Group</b>	<b>13.6</b>	<b>4.1</b>	<b>0.61 (not significant)</b>
<b>Intervention Group</b>	<b>16.7</b>	<b>4.1</b>	

SD: Standard Deviation  
(Mann-Whitney U test, p = 0.61)

### 3.4 SAFETY AND ADVERSE EVENTS

There were no adverse events documented in the intervention group and no patient died or withdrew from the study prematurely. No adverse events led to discontinuation or reduction in the enteral Intestamin® supplement in this group and all patients were able to tolerate the enteral supplement for the duration of the study.

## **CHAPTER 4:      DISCUSSION**

## **Study motivation and findings**

The motivation for this study arose out of the concept that certain nutritional supplements have expected benefits in critically ill patients because of their role in the immune response of the body to stress states, as the discussion in the preceding chapters has shown.<sup>5 7</sup> This is a particularly attractive concept, when the role of immune dysregulation in critical illness is considered. The results of this study have supported this benefit in some, but not all respects. The study has shown a statistically significant benefit in the patients, who received the immune supplement, only in the incidence of respiratory infections and the positive culture rates for tracheal aspirates and urinary catheter tip cultures, but has failed to show statistically significant differences between the intervention and control groups for other types of sepsis or for the ventilation time and time spent in ICU which were broadly considered to represent surrogate markers of the disease course. There were, in addition, statistically significant differences between the two groups with respect to the presence of pus cells in the sputum and urine which were higher in the intervention group and showed an inverse relationship with positive cultures. It is difficult to interpret this clinically and in isolation, but it may support a difference in the systemic immune response to infection between the two groups. Because pus cells are a marker for inflammation or infection, in the absence of a positive culture growth, it is tempting to speculate that the intervention group may be demonstrating an improved immune response.<sup>99</sup> Further study would be needed to clarify the significance of this relationship .

The failure to show improvement in overall sepsis rates, ventilation time and ICU stay is disappointing, but there are several factors in the design and implementation of the study which may have influenced these outcomes. The results, therefore, remain encouraging in supporting the role of early

immunonutrition supplements in this patient group. Although anecdotal, and open to the bias of an open label study, the clinicians involved in the trial felt that their patients made better progress in the intervention group and they were subsequently keen to implement more aggressive nutritional strategies in the future.

### **Study limitations**

In further considering the significance of the results, it is necessary to look critically at some of the limitations of the study which may have influenced the results and the likelihood of bias affecting the outcome.

As has been stated previously, this study must be considered as a pilot study only, not least because of the small numbers recruited and analysed. It is widely recognized that studies of enteral and parenteral nutrition require large numbers of patients to reach statistical significance because of the difficulties in studying critically ill patients in the ICU, the heterogeneous population of patients and the variables involved in disease-specific enteral and parenteral nutrition.. A large study group was not practicable in this study, because of limitations imposed by the size of the ICU in which the study was performed, the rate at which suitable patients presented to the unit and a fixed time frame for the study. Under these circumstances, the fact that any statistically significant differences were found, could be granted additional significance in support of the concept being tested. The numbers studied were insufficient to provide the statistical power needed and more robust conclusions could be expected from a much larger study group.

Additional bias may also be evident in the study design, in that it was open label, with the controls being identified and matched retrospectively. This was necessary again to maximize the available data from the intervention group. Had

both groups been studied prospectively in the same time frame, the study population would have been halved, with consequent exaggeration of the sample size limitations already discussed. So, to maximize patient numbers, the design was adapted. The strongest data however is derived from parallel double blinded studies where bias, related to uncontrolled differences between the two population groups, can be minimized and observer bias is also controlled.<sup>5 10</sup> If, for example, there were significant differences between the two groups in terms of treatment protocols, this would have affected the results. Intensive care is a dynamic specialty, and although protocols in this ICU have been standardized, in reality practices may change over a 23 month period, the time period which separated the controls from the intervention groups in this study. Bias, as result of this time lapse, cannot be ruled out .

The patients were chosen and matched according to disease-severity, based on APACHE scoring, which has been the basis of many other trials using ICU patients and correlates with outcome.<sup>5 60</sup> Despite this, the patients still manifest clinical heterogeneity. The patients in ICU are there because of the level of care they require, but are drawn from many subspecialities with associated comorbidities and pre-existing disease which will also influence the course of their illness. Thus medical patients may well behave differently from surgical patients, and trauma patients differently from elective patients, despite the illness severity scoring equally on the APACHE at the entry into the ICU.

In this area on the east coast of South Africa there is a high prevalence of HIV and AIDS among the patient population treated, indeed the highest in the country.<sup>100 101</sup> The prevalence of the infection is plateauing out according to epidemiological surveys, but between 2002 (first control patient in the study) and 2003 (last intervention patient in the study) there was a change in the prevalence

in Kwa Zulu Natal according to CDC statistics of up to 2%.<sup>100 101</sup> In such a small patient cohort, this could easily equate to a difference in prevalence of HIV positive patients in the two groups sufficient to influence the outcome parameters.

The issue of the effect of HIV status on the outcome in ICU is an interesting and complex one. In 1997 Bhagwanjee et al published a paper in the BMJ on the effect of HIV status on the outcome of patients admitted to the ICU.<sup>102</sup> The authors studied over 400 patients admitted to a large academic hospital ICU in Durban. They found no difference in the length of hospital or ICU stay or in mortality between HIV positive and negative patients, but they did find statistically significant differences between the two groups in morbidity, including a higher incidence of septic shock in HIV positive patients.<sup>102</sup> The two groups were not significantly different in respect to the APACHE scores, and therefore this will not differentiate between HIV positive and negative patients. More of the HIV positive patients came from orthopaedic and obstetric referrals, rather than medical referrals, which would again impact on the emergency trauma patient population and introduce possible bias in this group. There were no patients with apparently advanced immunosuppression and AIDS, the presence of which would be expected to influence the outcomes further and perhaps differently. So is it possible that a high HIV or AIDS rate detracted from the significance of the results in this study. There is no way of knowing, as this was not a parameter collected or indeed known in the majority of cases. However, bias associated with this factor cannot be excluded.

Upon reflection, the outcome measurements in this study need to be reconsidered. Using infection indicators as a single prognostic indicator in patients with multiple medical problems is simplistic and may not give the most

accurate indication of prognosis and outcome. More integrated scoring systems would offer a more accurate assessment. In 2008, Beale et al<sup>5</sup> published a study which investigated the effect of early enteral supplementation with Intestamin® on outcome in critically ill patients and they chose the outcome parameter of a compound score of sequential organ failure assessment, the SOFA score. The SOFA score is a score of six organ dysfunctions and can be applied sequentially in an ICU environment to chart the progress and assess prognosis. Both the mean, highest and change scores in SOFA scores are used as predictors of outcome in ICU and have shown to correlate well with morbidity and mortality. In the study by Beale the aim was to enroll 344 patients, but after the interim analysis of the first 50 patients the study was stopped. The results were overwhelmingly positive in favour of the Intestamin® group in terms of the improved SOFA scores, and continuing to enroll patients as placebo could not be justified ethically in the light of this finding. If a compound scoring system had been used in our study, it is tempting to speculate that the results may have been more strongly significant. Even with the strongly positive findings in Beales group, there was no difference between the groups for ICU/Hospital stay or infections, which mirrors the findings in our pilot study, but does not detract from the strongly positive benefits that they demonstrated on the SOFA scoring. Again this would suggest that the use of the length of ICU or hospital stay and even infection rates, as outcome parameters, may not be sensitive enough in identifying clinical benefit from Intestamin in a trial setting and why the endpoints in our pilot study were only partially met.<sup>5</sup>

### **Advantages of Intestamin®**

One of the advantages of Intestamin® is the small volume containing high doses of key nutrients. Thus the full volume of the supplement can be administered much sooner after admission into ICU. This is not possible with the old

generation enteral feeds. The manufacturer's recommendation is for a full 500mls to be administered from the first day of ICU stay and for 5 days thereafter. As this supplement was new at the time of our study, and the experience with the feed tolerance uncertain, the study aimed at introducing the full Intestamin® volume by the second ICU day. This was achieved in practice on day 1, the patients receiving between 105 and 483 mls of Intestamin®, but by day 2 and thereafter, all patients in the intervention group received 500 mls. At the end of 5 days of Intestamin®, the patients in the intervention group had received a total dose of Intestamin® of between 2105 and 2483 mls with a mean of 2294 mls, which is a mean short fall in the intended total Intestamin® dose of 206 mls. Whether this impacted negatively on the benefits is difficult to judge. Faster run rates and higher total volumes of the Intestamin® may achieve higher benefits. In the study by Beale et al, with strongly positive results in favour of the Intestamin® treated group, Intestamin® was continued for a 10 day period. Although 5 days is recommended as the Intestamin® supplement course by the manufacturers, the results from Beale et al suggest that the optimum duration of Intestamin® supplementation for the maximum benefits still needs to be determined.

### **Heterogenous population in ICU**

A final consideration in interpreting the results of this study must include the fact that Intestamin®, while having been developed to respond to many of the needs of an early enteral nutritional supplement, in respect of the feed volume and content, may not necessarily represent the best formulation for all patient groups. From the preceding discussion of the metabolic responses in critically stressed patients, it is clear that not all patients undergo the same changes in response to stress and this brings us back to the heterogenous population in the ICU. Different patients have different rates of nutrient depletion such as glutamine and antioxidants. Therefore different patients may need different doses in their

replacement. For example burn patients are recognised as having greater losses than those that occur in other types of trauma.<sup>58</sup> Error! Bookmark not defined. If this is considered, then it is clear that a generic supplement across all patient groups cannot possibly meet each patients need optimally, but rather will represent the best available compromise. Beale et al<sup>5</sup> measured the serum levels of several of the supplement constituents in the patient population receiving Intestamin® and in the controls and showed normalization of these parameters in the Intestamin® group, consistent with Intestamin® being a successful product for the treatment of these deficiencies, compared to the control group. This type of monitoring may allow the clinician to individualize the supplement to the patient's needs more efficiently and to allow for a range of runing rates, total duration or even a range of products to be chosen in the future.

This conclusion naturally relies on the assumption that the levels of these supplements, deemed normal in a normal population, reflect the correct levels for the increased needs in metabolic stress. The US Food and Nutrition Board defined NOAEL and LOAEL for antioxidant supplements on the levels associated with no adverse effects in a normal population.<sup>64</sup> These do not necessarily correlate with the levels needed in altered metabolic states, and again it is evident that there needs to be more clarification through further research, as the relative composition of these immunosupplements may well affect their potential benefit and may need to be disease-specific.

### **Tolerance of supplement**

The use of nasojejunal feeding in this study was associated with good tolerance of the Intestamin® supplement in the intervention group. This is perhaps not surprising in that nasojejunal feeding is recognised as a strategy to overcome enteral tolerance problems in this patient population.<sup>81</sup> It could be argued that nasojejunal feeding is the preferred route of enteral nutrition in the critically ill ICU patient especially in the early stages of enteral feeding.<sup>103 104 105</sup>

## **CHAPTER 5: CONCLUSION AND RECOMMENDATIONS**

## **5.1 CONCLUSIONS AND RECOMMENDATIONS**

This pilot study confirmed the tolerability of the supplement Intestamin®, administered to a population of critically ICU patients via the nasojejunal route and in combination with either TPN or enteral nutrition.

Furthermore, the use of Intestamin® early in this group was associated with measurable benefits in the rate of respiratory infection and positive sputum and urinary catheter tip cultures, despite results which showed no benefit in the rates of urinary infections, septicemia, hospital ventilation and ICU days. This can be seen as a possible indication that Intestamin® can be of benefit in decreasing nosocomial respiratory infections, specifically, in patients on ventilatory support.

Although Intestamin® supplementation did not result in conclusive benefits in the other end points studied in this intervention group, larger prospective studies with broader end points are recommended to clarify the remaining issues.

## **5.2 RECOMMENDATIONS**

The use of Intestamin® as a supplemental feed to TPN or enteral nutrition may be beneficial by improving the outcome of nosocomial infections in critically ill patients in an ICU setting.

Further investigations are needed, using this supplement, in a larger group of patients over a longer period of time, with alternative outcomes and controlling for patient variables in order to identify more accurately those patient groups most likely to benefit, and also to better understand the scope of the benefits. It is strongly suggested that different population groups are studied separately in formalized clinical trials.

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## ■ ADDENDA TO THESIS ■

# **The effect of Intestamin® administration to critically ill patients on the prevalence of infection, ventilation requirements and duration of Intensive care unit stay: A Pilot Study**

Thesis presented in partial fulfillment of the requirements for the degree of Master of Nutrition at University of Stellenbosch

By

Hester S van Niekerk (Tersia)

## **LIST OF ADDENDA**

- Addendum A:      Generating the APACHE II Score
- Addendum B:      Biochemical Data collection Form
- Addendum C:      Ethics approval letter from University of Stellenbosch
- Addendum D:      Consent form
- Addendum E:      The Bay

Thesis presented in partial fulfillment of the requirements for the degree of Master of Nutrition at University of Stellenbosch

By

Hester S van Niekerk (Tersia)

## **Addendum A**

## Generating the APACHE II Score

### Overview:

The APACHE II score is a general measure of disease severity based on current physiologic measurements age and previous health condition. The score can help in the assessment of patients to determine the level and degree of diagnostic and therapeutic intervention.

Components:

(1) acute physiology score (APS)

(2) age points

(3) chronic health points

Data collection:

- The data for the acute physiology is collected during the initial 24 hour period after ICU admission.
- The worst (most deranged) physiologic value is selected for grading.

## Acute Physiology Score (APS)

Parameter	Finding	Points	-1	1	2	3	4	5
rectal temp in C°	>= 41	+4						
	39-40.9	+3						
	38.5-38.9	+1						
	36-38.4	0						
	34-35.9	+1						
	32-33.9	+2						
	30-31.9	+3						
<= 29.9	+4							
mean arterial pressure mm Hg	>= 160	+4						
	130-159	+3						
	110-129	+2						
	70-109	0						
	50-69	+2						
<= 49	+4							
heart rate in beats/minute	>= 180	+4						
	140-179	+3						
	110-139	+2						
	70-109	0						
	55-69	+2						
	40-54	+3						
<= 39	+4							
respiratory rate in breaths/min	>=50	+4						
	35-49	+3						
	25-34	+1						
	12-24	0						
	10-11	+1						
	6-9	+2						
	<= 5	+4						
oxygenation	A-aDO2 >= 500 and FIO2 >= 0.5	+4						
	A-aDO2 350-499 and FIO2 >= 0.5	+3						
	A-aDO2 200-349 and FIO2 >= 0.5	+2						
	A-aDO2 < 200 and FIO2 >= 0.5	0						
	PaO2 > 70 and FIO2 < 0.5	0						
	PaO2 61-70 and FIO2 < 0.5	+1						
	PaO2 55-60 and FIO2 < 0.5	+3						
PaO2 < 55 and FIO2 < 0.5	+4							
arterial pH	>= 7.7	+4						
	7.6-7.69	+3						
	7.5-7.59	+1						
	7.33-7.49	0						

Parameter	Finding	Points	-1	1	2	3	4	5
	7.25-7.32	+2						
	7.15-7.24	+3						
	< 7.15	+4						
serum sodium	>= 180	+4						
	160-179	+3						
	155-159	+2						
	150-154	+1						
	130-149	0						
	120-129	+2						
	111-119	+3						
<= 110	+4							
serum potassium	>= 7.0	+4						
	6.0-6.9	+3						
	5.5-5.9	+1						
	3.5-5.4	0						
	3.0-3.4	+1						
	2.5-2.9	+2						
	< 2.5	+4						
serum creatinine in mg/dL	>= 3.5 and not acute renal failure	+4						
	2.0-3.4 and not acute renal failure	+3						
	1.5-1.9 and not acute renal failure	+2						
	0.6-1.4 and not acute renal failure	0						
	< 0.6 and not acute renal failure	+2						
	>= 3.5 and acute renal failure	+8						
	2.0-3.4 and acute renal failure	+6						
	1.5-1.9 and acute renal failure	+4						
	0.6-1.4 and acute renal failure	0						
< 0.6 and acute renal failure	+4							
hematocrit in percent	>= 60	+4						
	50-59.9	+2						
	46-49.9	+1						
	30-45.9	0						
	20-29.9	+2						
	< 20	+4						
WBC count in thousands	>= 40	+4						
	20-39.9	+2						
	15-19.9	+1						
	3-14.9	0						
	1-2.9	+2						
	< 1	+4						
Glasgow Coma Score		15 -						

where:

- The score for serum creatinine is doubled if the patient has acute renal failure.
- mean arterial pressure = ((systolic blood pressure)+ (2 \* (diastolic pressure))) / 2

If no blood gas data is available then the serum bicarbonate can be used ( assume in place of the arterial pH):

Parameter	Finding	Points	-1	1	2	3	4	5
serum bicarbonate in mmol/L	>= 52.0	+4						
	41.0 – 51.9	+3						
	32.0 – 40.9	+1						
	22.0 – 31.9	0						
	18.0 – 21.9	+2						
	15.0 – 17.9	+3						
	< 15.0	+4						

### Age Points

Age	Points
<= 44	0
45-54	2
55-64	3
65-74	5
>= 75	6

### Chronic Health Points

Operative Status	Health Status	Points
Non-operative patient	history of severe organ insufficiency OR immune compromised	5
	no history of severe organ insufficiency AND immune competent	0
Emergency postoperative patient	history of severe organ insufficiency OR immune compromised	5
	no history of severe organ insufficiency AND immune competent	0
Elective postoperative patient	history of severe organ insufficiency OR immune compromised	2
	no history of severe organ insufficiency AND immune competent	0

where:

- ❖ organ insufficiency or immune compromised state must have preceded the current admission
  
- ❖ immune compromised if:
  - (1) receiving therapy reducing host defenses (immune suppression chemotherapy radiation therapy long term steroid use high dose steroid therapy) or
  - (2) has a disease severe enough to interfere with immune function such as malignant lymphoma leukemia or AIDS
  
- ❖ liver insufficiency if:
  - (1) biopsy proven cirrhosis
  - (2) portal hypertension
  - (3) episodes of upper GI bleeding due to portal hypertension (4) prior episodes of hepatic failure coma or encephalopathy
  
- ❖ cardiovascular insufficiency if:
  - (1) New York Heart Association Class IV
  
- ❖ respiratory insufficiency if:
  - (1) severe exercise restriction due to chronic restrictive obstructive or vascular disease;
  - (2) documented chronic hypoxia hypercapnia secondary polycythemia severe pulmonary hypertension; and
  - (3) respirator dependency
  
- ❖ renal insufficiency if:
  - (1) on chronic dialysis

## APACHE II SCORE

Apache Score = (acute physiology score) + (age points) + (chronic health points)

Interpretation:

- minimum score: **0**
- maximum score: **71**
- An increasing score is associated with an increasing risk of hospital death.

### **References:**

Knaus WA Draper EA et al. APACHE II: A severity of disease classification system. Critical Care Medicine. 1985; 13

## Computing the Predicted Death Rate for Acutely Ill Patients with APACHE II

### Overview:

From the APACHE II score and knowledge of primary clinical diagnoses an estimated risk of death in the hospital can be calculated.

R = estimated risk of hospital death

$\ln \left( \frac{R}{1 - R} \right) = (-3.517) + (0.146 * (\text{APACHE II score})) + (0.603 \text{ if post-emergency surgery } 0 \text{ if not}) + (\text{diagnostic category weight})$

### Diagnostic Category - Nonoperative

Group	Disorder	Weight
<b>respiratory failure or insufficiency</b>	asthma or allergy	-2.108
	COPD	-0.367
	pulmonary edema noncardiogenic	-0.251
	post-respiratory arrest	-0.168
	aspiration	-0.142
	poisoning or toxic	-0.142
	pulmonary embolus	-0.128
	infection	0
	neoplasm	0.891
<b>cardiovascular failure or insufficiency</b>	hypertension	-1.798
	rhythm disturbance	-1.368
	congestive heart failure	-0.424
	hemorrhagic shock or hypovolemia	0.493
	coronary artery disease	-0.191
	sepsis	0.113
	postcardiac arrest	0.393
	cardiogenic shock	-0.259
<b>trauma</b>	multiple trauma	-1.228
	head trauma	-0.517
<b>neurologic</b>	seizure disorder	-0.584
	ICH/SDH/SAH	0.723
<b>other</b>	drug overdose	-3.353

Group	Disorder	Weight
	diabetic ketoacidosis	-1.507
	GI bleeding	0.334
vital organ affected	metabolic or renal	-0.885
	respiratory	-0.890
	neurologic	-0.759
	cardiovascular	0.470
	gastrointestinal	0.501

### Diagnostic Category - Operative

Group	Disorder	Weight
Operation	multiple trauma	-1.684
	chronic cardiovascular disease	-1.376
	peripheral vascular disease	-1.315
	heart valve surgery	-1.261
	craniotomy for neoplasm	-1.245
	renal surgery for neoplasm	-1.204
	renal transplant	-1.042
	head trauma	-0.955
	thoracic surgery for neoplasm	-0.802
	craniotomy for ICH/SDH/SAH	-0.788
	laminectomy or other spinal cord surgery	-0.699
	hemorrhagic shock	-0.682
	GI bleeding	-0.617
	GI surgery for neoplasm	-0.248
	respiratory insufficiency after surgery	-0.140
GI perforation or obstruction	0.060	
Postoperative complications	sepsis	0.113
	Post cardiac arrest	0.393
	Post respiratory arrest	-0.168
NOS	neurologic	-1.150
	cardiovascular	-0.797
	respiratory	-0.610
	gastrointestinal	-0.613
	metabolic renal	-0.196

**References:**

Knaus WA Draper EA et al. APACHE II: A severity of disease classification system. Critical Care Medicine. 1985; 13 (Appendix pages 828-829)

## **Addendum B**

BIOCHEMICAL VALUES					
Subject:		Date:		ICU Day no	Originator
TESTS	RESULTS	UNIT	Reference Values		NOTES
			MALE	FEMALE	
<b>UREA/ELECTROLYTES</b>					
SODIUM		mmol/l	133-	145	
POTASSIUM		mmol/l	3.7-	5	
CHLORIDE		mmol/l	95-	110	
BICARBONATE		mmol/l	20-	30	
UREA		mmol/l	2.5-	6.8	
CREATININE		mmol/l	63-115	53-97	
OSMOLALITY-S		mOsm/kg	286-	294	
OSMOLALITY-U		mOsm/kg	50-	1200	
<b>LIVER FUNCTIONS</b>					
ALPKHOS		U/l	92	287	
GAMMAGT		U/l	10-49	6-32	
AST(SGOT)		U/l	0-39	0-32	
ALT(SGPT)		U/l	0-40	0-31	
TOTAL L D H		U/l	174	464	
TOT. BILIRUBIN		mmol/l	2	17	
DIR. BILIRUBIN		mmol/l	0-	8.5	
TOTAL PROTEIN		g/l	63	78	
ALBUMIN		g/l	36-	52	
SERUM CALCIUM (Corrected)		mmol/l	2.02-	2.6	
PHOSPHATE		mmol/l	0.8-	1.6	
MAGNESIUM		mmol/l	0.70-	1.07	
<b>BLOOD GAS</b>					
pH			7.360 -	7.42	
pCO <sub>2</sub>		kPa	4.77-	6.19	
pO <sub>2</sub>		kPa	11.97 -	14.63	
STD. BICARB		mmol / l	22 -	26	
BASE EXCESS		mmol / l	-24 : +2.3 -	-3.3: +1.2	
O <sub>2</sub> SAT		%		100	
<b>FULL BLOOD COUNT</b>					
Hb		g/dl	13.0-18.0	11.5-16.5	
RBC		X10 <sup>12</sup> /l	4.5-6.5	3.8-5.8	
PCV(HCT)		l	0.40-0.54	0.37-0.46	
MCV		f	76-96		
MCH					
MCHC					
RDW					
PLATELETS		x10 <sup>9</sup> /l	150-	400	
WBC		x10 <sup>9</sup> /l	4.0-	11	
<b>COAGULATION</b>					
INR(PI)			0.8	-1.2	
PTT		sec	25	-40	
GLUCOSE-RANDOM		mmol/l			
<b>ICU AND VENTILATOR DAYS</b>					
DAYS IN ICU		days			
VENTILATOR DAYS		days			
<b>NOSOCROMAL INFECTIONS EVALUATION</b>					
<b>CLINICAL INDICATION OF INFECTION</b>					
TEMPERATURE (AXILLA)		°C	36-37		
HEART RATE		beats/min	>90		
RESPIRATORY RATE		breaths/min	>20		
HYPOTENSION		mmHg	<90mmHg		
OLIGURIA					
ACUTE ALTERATION IN MENTAL STATUS		gcs			
<b>LABORATORY INDICATION OF INFECTION</b>					
LINE TIP CULTURES					
STOOL CULTURES					
BLOOD CULTURES					
WBC		cells/mm <sup>3</sup>	>12000		
URINE CULTURES					

## **Addendum C**



UNIVERSITEIT • STELLENBOSCH • UNIVERSITY  
jou kennisvenoot • your knowledge partner

26 October 2004

Ms HS van Niekerk  
Department of Human Nutrition

Dear Ms Van Niekerk

**RESEARCH PROJECT: "INVESTIGATING THE EFFECT OF INTESTAMIN®  
ADMINISTRATION TO CRITICALLY ILL PATIENTS ON  
THE PREVALENCE OF INFECTION, VENTILATION  
REQUIREMENTS AND DURATION OF HOSPITAL STAY"**

**PROJECT NUMBER : N04/10/166**

It is my pleasure to inform you that the abovementioned project has been approved and that you may start with the project. This approval will however be submitted at the next meeting of the Committee for Human Research for ratification, after which we will contact you again.

Notwithstanding this approval, the Committee can request that work on this project be halted temporarily in anticipation of more information that they might deem necessary to make their final decision.

In future correspondence, kindly refer to the above project number.

I wish to remind you that patients participating in a research project at Tygerberg Hospital will not receive their treatment free, as the PGWC does not support research financially.

The nursing staff of Tygerberg Hospital can also not provide extensive nursing aid for research projects, due to the heavy workload that is already being placed upon them. In such instances a researcher might be expected to make use of private nurses instead.

Yours faithfully

**CJ VAN TONDER**  
**RESEARCH DEVELOPMENT AND SUPPORT (TYGERBERG)**

CJVT/ev

cc: Prof D Labadarios

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## **Addendum D**

# INFORMATION AND INFORMED CONSENT DOCUMENT

TITLE OF THE RESEARCH PROJECT:

**A STUDY OF THE EFFECT OF INTESTAMIN® ADMINISTRATION TO CRITICALLY ILL PATIENTS ON THE PREVALENCE OF INFECTION, VENTILATION REQUIREMENTS AND DURATION OF HOSPITAL STAY.**

REFERENCE NUMBER: .....

PRINCIPAL INVESTIGATOR: **Mrs HS VAN NIEKERK, RD(SA)ADE,  
DR G KELLING, SPECIALIST SURGEON,  
DR P VAN ROOYEN, SPECIALIST SURGEON**

(hereinafter referred to as "Investigators")

ADDRESS: **PO BOX 41357,  
RICHARDS BAY  
3900**

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## **DECLARATION BY OR ON BEHALF OF PARTICIPANT:**

I, the undersigned, BARBARA MOORE. (*name*)

[ID No: **5708300270082** in my capacity as **THE HOSPITAL MANAGER** of the patients as listed in Annexure "A"

### **A. HEREBY CONFIRM AS FOLLOWS:**

1. I was invited to participate in the abovementioned research project which is being undertaken by the Investigators in collaboration with the Department of Human Nutrition, Faculty of Health Sciences, Stellenbosch University for the purpose of completing a Masters Degree in Human Nutrition for Mrs. HS van Niekerk.
2. The following aspects have been explained to me:
  - 2.1 **Aim:** The purpose of this study is to determine the effect of Intestamin® administration to critically ill patients on the prevalence of infection, ventilation requirements and duration of hospital stay determining if Intestamin® decrease nosocomial infection (lung, urine and linesepsis) rate in the critically ill, ventilation days in the critically ill, and the length of stay in ICU. The hypothesis of this study then is to determine if Intestamin® administered to the critically ill patients will have beneficial effects on the prevalence of infection, ventilation requirements and duration of ICU stay.
  - 2.2 **Procedures:** The study design covers a retrospective, case control, analytical study of patients that have been admitted to ICU (The Bay Hospital) and treated with Intestamin ® during June 2003 until November 2003 and a literature overview. These results will be compared with patients (control group) with similar conditions that were admitted in ICU (The Bay Hospital) during the period from January 2002 until end off May 2003 (comparative period), and which were not treated with Intestamin®. These two groups could be compared as there was no protocol change in the management off patients in ICU during the mentioned periods. The diagnostic criteria and treatment procedures would stay the same, except for the use off Intestamin ® in the intervention group.

- 2.3 **Risks:** As the study only compares and is retrospective in terms of patients treated with Intestamin ® and those not treated with Intestamin ®, also considering that Intestamin ® was only introduced in June 2003, no risk exists.
- 2.5 **Benefits:** The preliminary results of the study indicate that there could be clear benefits in terms of the effects on the prevalence of infection, ventilation requirements and duration of ICU stay.
- 2.6 **Confidentiality:** The information collected will be treated as confidential, it will be included in a thesis, and publication in a professional journal, without disclosing the identity of the patients.
3. The information above was explained to me by a representative of the Investigators in English and I am in command of this language. I was given the opportunity to ask questions and all these questions were answered satisfactorily.
4. No pressure was exerted on me to consent to participation and I understand(s) that I may withdraw at any stage without any penalization.

**B. I HEREBY BY THE AUTHORITY VESTED IN ME AS THE BAY HOSPITAL MANAGER GIVE CONSENT THAT THE LISTED ICU PATIENT(S) DISEASE MANAGEMENT INFORMATION AND ALL RELEVANT INFORMATION REQUIRED FOR THE ABOVEMENTIONED STUDY BE USED**

Signed/confirmed at RICHARDS BAY on 26 AUGUST 2004  
 (place) (date)

  
 Signature

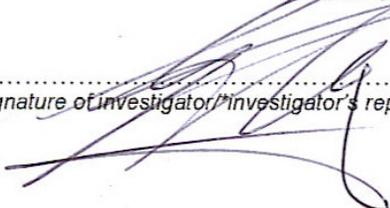
  
 Signature of witness

**C. STATEMENT BY OR ON BEHALF OF INVESTIGATOR(S):**

I, **Dr G KELLING** as designated representative on behalf of the Investigators for the purpose of obtaining consent from the Participant declare that:

- I explained the information given in this document to the Participant, **THE HOSPITAL MANAGER** ;
- The Participant, **THE HOSPITAL MANAGER** was encouraged and given ample time to ask me any questions;
- This conversation was conducted in English and no translator was used.

Signed at RICHARDS BAY on 26/8/2004 2004  
 (place) (date)

  
 Signature of investigator/ investigator's representative

  
 Signature of witness

**IMPORTANT MESSAGE TO PATIENT/\*REPRESENTATIVE OF PARTICIPANT:**

Dear participant,

Thank you for THE BAY HOSPITALS participation in this study. Should, at any time during the study,

- an emergency arise as a result of the research, or
- you require any further information with regard to the study, kindly contact:

**Mrs HS van Niekerk** at telephone number **083 460 7591**.

## **Addendum E**

## The Bay Hospital ICU Feeding protocol

Day count	Patient nutritional needs (25kcal/kg/day)	Total Parental Nutrition (TPN) running rate / hour	Hours	Intestamin running rate / hour	Standard Enteral feed running rate / hour (disease specific)	Nasogastric aspirate (ml) after no enteral feed for 1 hour
<b>1</b>	Patient specific	Disease specific	1	10		Nil
		94	4	15	0	Nil
		80	8	22	0	Nil
		60	12	33	30	Nil
		50	16	50	50	Nil
				24		
<p><i>After 4 hours of enteral feeding, stop feed for 1 hour and do enteral nasogastric aspirate. If Aspirate less than 50% of total enteral intake then increase with 50%, if aspirate equal the amount enteral intake keep at the same running rate, if aspirate &gt; 50% of total enteral intake then decrease running rate with 50 %.</i></p>						
<b>2</b>			1			
			4			
			8			
			12			
			16			
			24			
<b>3</b>			1			
			4			
			8			
			12			
			16			
			24			
<b>4</b>			1			
			4			
			8			
			12			
			16			
			24			
<b>5</b>			1			
			4			
			8			
			12			
			16			
			24			

