THE IMPACT OF INTRAVENOUS FLUID AND ELECTROLYTE ADMINISTRATION ON TOTAL FLUID, ELECTROLYTE AND ENERGY INTAKE IN CRITICALLY ILL ADULT PATIENTS

by

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"DECLARATION"

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ABSTRACT

Objectives: The objectives of this study were to determine the nutritional content/ contribution of intravenous (IV) fluid and electrolyte administration on the total feeding prescription of intensive care unit (ICU) patients.

Methods: Retrospective review of ICU charts of consecutive patients (>18 years) with APACHE II scores ≥10 and on ≥72 hours nutrition therapy (NT) admitted to a medical/surgical ICU. Total fluid, electrolyte, energy and macronutrient intake from nutritional and non-nutritional sources were reviewed from ICU admission until discharge, discontinuation of NT or death for ≤7 days. Energy and protein delivery were compared to calculated targets of 25.4 – 28.6kCal/kg and 1.3 – 1.5g/kg respectively. Summary statistics, correlation coefficients and appropriate analysis of variance were used to describe and analyse the data.

Results: A total of 71 patients (49% male), average age 49.2 ± 17.1, average APACHE II score 21.0 ± 6.1, 68% medical and 32% surgical, were included. Fluid and nutrient intake were reviewed over a mean of 5.7 ± 1.1 days.

Mean daily fluid delivery was 3.2 ± 0.6L. IV fluid therapy (IVFT) contributed 32.0 ± 12.0% to total fluid delivery (TFD), whereas IV drug administration, including fluids used for reconstitution and dilution purposes, contributed 20.7 ± 8.1% to TFD.

Balanced electrolyte solutions (BES) were the crystalloid of choice, prescribed in 91.5% of patients with a mean daily volume (MDV) of 0.5 ± 0.4L. Hypertonic low molecular weight (LMW) 130/0.4kD hydroxyethyl starch (HES) was the colloid of choice, prescribed in 78.9% of patients with a MDV of 0.2 ± 0.1L. Potassium salts were the most frequently prescribed IV electrolyte supplement (IVES), prescribed in 91% of patients (±20 – 60mmol per administration).

NT was initiated within 14.5 ± 14.1 hours. The majority (80%) received enteral nutrition (EN). The mean daily energy delivered was 1613 ± 380kCal (25.1kCal/kg), meeting 93.6 ± 17.7% of mean target range (MTR). Mean daily protein delivery (PD) was 72 ± 22g (1.1g/kg), meeting 82.8 ± 19.9% of MTR. Non-nutritional energy sources (NNES), mostly derived from carbohydrate-containing IV fluids, contributed 10.1 ± 7.5% to total energy delivered (156kCal/d). Mean cumulative energy and protein balance was -674.0 ± 1866.1kCal and -86.0 ± 106.9g respectively. The majority (73%) received >90% of the minimum energy target but only 49% >90% of minimum protein target; 59% of those with energy intake 90-110% of target had adequate protein intake. A significant negative correlation was found between cumulative energy/protein balance and the time to initiation of NT (energy: r=-0.28, p=0.02; protein: r=-0.32, p=0.01).

Conclusion: In this ICU BES are the crystalloid of choice and hypertonic LMW 130/0.4kD HES the colloid of choice for IVFT. Potassium salts are the most frequently prescribed IVES. NNES added

significantly to energy delivery and should be included in the calculation of feeding prescriptions to avoid the harmful effects of overfeeding. Early initiation of EN with conventional products which are energy rich is insufficient to achieve adequate PD. EN formulae with a more favorable nitrogen to non-protein energy ratio could help to optimise PD during the first week of ICU care.

OPSOMMING

Doelwitte: Die doelwit van hierdie studie was om die voedingswaarde/ bydrae van intraveneuse (IV) vog en elektroliet toediening tot die totale voedings voorskrif van pasiënte in ‘n intensiewe sorg eenheid (ISE) te bepaal.

Metodes: Retrospektiewe bestudering van die ISE kaarte van agtereenvolgende pasiënte (>18 jaar) opgeneem in ‘n mediese/chirurgie ISE en met APACHE II tellings ≥10 en ≥72 ure voedingsterapie (VT). Totale vog, elektroliet, energie en makronutriënt inname vanaf voedingsverwante en nie-voedingsverwante bronne is vanaf ISE opname tot en met ontslag, staking van VT of sterfte, vir ≤7 dae hersien. Energie en proteiën inname is vergelyk met berekende doelwitte van 25.4 – 28.6kKal/kg en 1.3 – 1.5g/kg onderskeidelik. Beskrywende statisitiek, korrelasie koeffisiënte en toepaslike analises van variansie is gebruik vir data analise.

Resultate: 71 pasiënte (49% mans), gemiddelde ouderdom 49.2 ± 17.1, gemiddelde APACHE II telling 21.0 ± 6.1, 68% medies en 32% chirurgie, is ingesluit. Vog en voedingstof inname is hersien oor ‘n gemiddelde tydperk van 5.7 ± 1.1 dae. Gemiddelde vog inname was 3.2 ± 0.6L/dag. IV vog terapie (IVVT) het 32.0 ± 12.0% bygedra tot totale vog inname (TVI). IV medikasie toediening, insluitende die herkonstruksie en verwatering van medikasie, het 20.7 ± 8.1% bygedra tot TVI.

Die mees voorgeskrewe kristalloiëd en kolloiëd vir IVVT was gebalanseerde elektroliet oplossings (GEO), voorgeskryf in 91.5% van pasiënte (gemiddeld 0.5 ± 0.4L/dag), en hipertoniese lae molekulêre gewig (LMG) 130/0.4kD hidroksie-etiel stysel (HES), voorgeskryf in 78.9% van pasiënte (gemiddeld 0.2 ± 0.1L/dag), onderskeidelik. Die mees voorgeskrewe IV elektroliet supplement was kalium soute, voorgeskryf in 91% van pasiënte (±20 – 60 mmol per toediening).

VT is binne 14.5 ± 14.1 ure geinisieër. Die meerderheid (80%) het enterale voeding (EV) ontvang. Die gemiddelde daaglikse energie inname van 1613 ± 380kCal (25.1kKal/kg) het 93.6 ± 17.7% van die gemiddelde doelwit rykwydte (GDR) bereik. Die gemiddelde daaglikse proteiën inname van 72 ± 22g (1.1g/kg) het 82.8 ± 19.9% van die GDR bereik. Nie voedings-verwante energie bronne (NVEB), meestal vanaf koolhidraat-bevattende IV vloeistowwe, het 10.1 ± 7.5% tot totale energie inname (TEI) bygedra (156kKal/d). Die gemiddelde kumulatiewe energie en proteiën balans was -674.0 ± 1866.1kKal en -86.0 ± 106.9g onderskeidelik. Die meerderheid (73%) het >90% van die minimum energie doelwit (ED) bereik. Slegs 49% het >90% van die minimum proteiën doelwit (PD) bereik. Slegs 59% van pasiënte met genoegsame energie inname (90-110% van ED) het hul minimum PD bereik. Daar was ‘n beduidende negatiewe korrelasie tussen kumulatiewe energie/proteiën balans en die tyd tot inisiëring van VT (energie: r=-0.28, p=0.02; proteiën: r=-0.32, p= 0.01).

Opsomming: Die kristalloiëd en kolloiëd van keuse vir IVT is GEO en hipertoniese LMG 130/0.4kD HES onderskeidelik. Kalium soute word mees algemeen voorgeskryf. NVEB dra beduidend by tot TEI en moet inaggeneem word tydens die berekening van voedingsvoorskrifte ten einde oorvoeding te voorkom. Vroeë inisiëring van EV met konvensionele energie-ryke EV produkte is onvoldoende om genoegsame proteiën inname te verseker. EV produkte met ‘n gunstiger stikstof tot nie-proteiën energie verhouding sal help om proteiën inname gedurende die eerste week van intensiewe sorg te optimaliseer.

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CONTRIBUTIONS BY PRINCIPAL RESEARCHER & CO-RESEARCHERS

The principal researcher was responsible for protocol compilation, study planning and execution, data collection, data entry, data analysis with the help of a statistician and writing up of the thesis. The co-researchers provided guidance regarding the research process. No fieldworkers were used.

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LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
ACS	Abdominal compartment syndrome
ADH	Anti-diuretic hormone
ANOVA	Analysis of variance
APACHE II	Acute Physiology and Chronic Health Evaluation II scoring system
AKI	Acute kidney injury
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
ASPEN	American Society of Parenteral and Enteral Nutrition
BEE	Basal energy expenditure
BMI	Body mass index
CCPG	Canadian Clinical Practice Guidelines
CHO	Carbohydrates
CO	Cardiac output
CRRT	Continuous renal replacement therapy
CVP	Central venous pressure
ECF	Extracellular fluid
EG	Endothelial glycocalyx
EN	Enteral nutrition
ERAS	Enhanced Recovery After Surgery
ESPEN	European Society of Parenteral and Enteral Nutrition
GIT	Gastrointestinal
HES	Hydroxyl-ethyl starch
IC	Indirect calorimetry
IBW	Ideal body weight
ICF	Intracellular fluid
ICU	Intensive care unit
IV	Intravenous
IVES	Intravenous electrolyte supplements
IVFT	Intravenous fluid therapy
LBM	Lean body mass
LMW	Low molecular weight
LDL	Low-density lipoprotein

LIST OF ABBREVIATIONS

LPS	Lipopolysaccharide
MTR	Mean target range
MW	Molecular weight
PEM	Protein energy malnutrition
PN	Parenteral nutrition
NICE	National Institute for Health and Clinical Excellence
NNES	Non-nutritional energy sources
NPE	Non-protein energy
NPO	Nil per os
NRF	Normal renal function
NT	Nutrition therapy
PN	Parenteral nutrition
PPV	Pulse-pressure variations
RAAS	Renin-angiotensin-activating-system
RCT	Randomised controlled trial
RD	Registered dietician
RFS	Refeeding syndrome
RRT	Renal replacement therapy
SAFE	Saline versus Albumin Fluid Evaluation study
SCCM	Society of Critical Care Medicine
SIRS	Systemic inflammatory response syndrome
SLED	Sustained low efficiency dialysis
SOAP	Sepsis Occurrence in Acutely Ill Patients
SPV	Systolic pressure variations
TBI	Traumatic brain injury
TBW	Total body water
TED	Total energy delivery
TF	Trophic feeding
TFD	Total fluid delivery
TG	Triglycerides
TNF	Tumour necrosis factor

DEFINITION OF TERMS

APACHE II score	A scoring system for use in ICU patients to assess the severity of disease and provide an estimation of in-hospital mortality.[1]
Colloid	A solution composed of larger, more insoluble molecules that do not readily cross semipermeable membranes [2] and can either be semi-synthetic or naturally occurring human plasma derivatives.[3]
Crystalloid	A solution consisting of small water-soluble molecules that can easily diffuse across semi-permeable membranes and with ion concentrations equal or close to to that of the extracellular space.[2,4]
Dipeptiven	A concentrate of the dipeptide N(2)-L-alanyl-L-glutamine indicated as part of an intravenous nutrition regimen as a supplement to amino acid solutions.[5]
Enteral nutrition	Nutrition provided through the gastrointestinal tract via a tube, catheter or stoma that delivers nutrients distal to the oral cavity.[6]
Intravenous drug dilution	Dilution of certain intravenous drugs to prevent irritation of veins. These medications are diluted according to the pharmacy references and administered intermittently or continuously.[7]
Intravenous electrolyte supplements	Intravenous infusion of electrolyte preparations (e.g. potassium phosphate, calcium gluconate and magnesium sulphate).[8]
Intravenous fluids	Fluids that are administered intravenously.[9]
Intravenous fluid therapy	The administration of intravenous fluids; namely crystalloids, colloids and blood products, to achieve and maintain hemodynamic stability and optimise organ function.[3,10]
Intravenous infusion	The slow intravenous injection of a substance. This is a common method for replacing water, electrolytes, and blood products and is also used for the continuous administration of drugs (e.g. antibiotics) or nutrition.[9]

DEFINITION OF TERMS	
Nutrition therapy	The provision of nutrients via an artificial route, i.e. enteral and/or parenteral nutrition.[11] Nutrient provision is no longer regarded as supportive care in ICU, but rather as a therapeutic intervention.[12]
Parenteral nutrition	Provision of nutrients intravenously.[13]
Polygam	Polyvalent human normal immunoglobulin used in the treatment of Guillian-bare syndrome. Polygam contains sucrose as stabiliser.[14]
Propofol	An intravenous sedative-hypnotic agent administered as a lipid emulsion for the induction and maintenance of anesthesia or for sedation of critically ill patients in the ICU.[15,16]
Recumbent height	A patient's body is aligned so that the lower extremities, trunk, shoulders, and head are in a straight line. A mark is made on the bed sheet at the base of the heels and top of the crown. The distance between these two lines is measured using a non-elastic tape measure.[17]
Sepsis	The systemic inflammatory response syndrome (SIRS) in the presence of infection.[18]
Septic shock	The presence of severe sepsis and hemodynamic instability.[18]
Severe sepsis/SIRS	The presence of sepsis/SIRS with one or more organ dysfunction.[18]
SIRS	A clinical syndrome that can be caused by a variety of insults, including infection, severe trauma, pancreatitis, ischemia, and burn injury. It is characterized by fever, tachycardia, tachypnoea, and an elevated white cell count as well as organ dysfunction and hypotension in severe cases.[18]

CHAPTER 1
INTRODUCTION AND MOTIVATION

1.1 Significance of the study

Critical illness encompasses a wide range of physiological abnormalities that are related to impaired fluid regulation, hence putting the critically ill patient at risk of fluid and electrolyte imbalance.[10] Intravenous (IV) fluid and volume management play a crucial role in achieving and maintaining this balance,[10,19] however, intensive care unit (ICU) physicians do face daily difficulty in management of fluid status.[20] This is of concern to the ICU dietician, since nutrition therapy (NT) and fluid and electrolyte balance are closely related in critical illness.[21-22]

Fluid and electrolyte status is influenced, purposefully or involuntarily, by the provision of NT.[23] Likewise, the delivery and tolerance of NT is influenced by a patient's fluid and electrolyte status. Published evidence suggests that fluid overload delays gastric emptying and intestinal transit time, prolongs post-operative ileus and delays achievement of nutritional targets.[21-22] On the other hand, severe acute hypovolemia is associated with impaired microvascular blood flow in vascular beds such as the splanchnic circulation,[23] resulting in decreased tolerance of enteral nutrition (EN). Fluid and electrolyte balance also play an important role in patients fed via the parenteral route and determination of fluid status is a prerequisite for calculating parenteral nutrition (PN) fluid requirements, especially if a fluid imbalance is clinically suspected.[24]

Achieving and maintaining fluid and electrolyte balance therefore plays a crucial role in obtaining the full benefit from EN and/or PN.[22] Daily monitoring of fluid and electrolyte status, as well as determination of fluid and electrolyte requirements will assist in the successful management of patients receiving NT.[25] Fluid and electrolyte intake via the parenteral, enteral and oral route should be considered to ensure timely and appropriate adjustment of the volume or electrolyte content of NT regimens.[24] Assessing input and output charts provide valuable information on fluid status, however, frequent errors in the measurement and recording of specific volumes, combined with a failure to estimate insensible losses, often results in a large cumulative error in fluid balance.[25-26] Furthermore, IV electrolyte replacement, a routine ICU practice, lacks standardization, and the dosing, timing and monitoring of electrolyte replacement varies considerably from clinician to clinician.[27] The volume and composition of IV fluids used for IV drug dilution and flushing of IV lines may also impact on total daily fluid and electrolyte intake. There is currently a lack of studies with an accurate assessment of total fluid and electrolyte delivery via all routes, including additional fluid delivery from drug administration (i.e. liquid drugs, fluids used for reconstitution and dilution purposes), as well as flushing of IV lines.

IV fluid therapy (IVFT) and drug administration not only influences total fluid and electrolyte intake, but also total energy intake. The extent to which such routine ICU practices contribute to total energy intake is of concern as there is strong evidence that overfeeding negatively impacts on

clinical outcomes.[28-30] Several previous studies that have assessed energy intake among critically ill patients failed to take into account additional energy delivery from inadvertent non-nutritional energy sources (NNES). According to a recent review article by Berger and Pichard [29] the concept of counting only non-protein energy (NPE), as well as failing to take into account the energy derived from NNES, such as glucose 5% solutions and fat soluble sedatives, might have been responsible for systematic overfeeding in several studies. Several authors have therefore suggested that the energy content of inadvertent NNES should be taken into account when prescribing energy targets.[29,31-32]

Heidegger et al [32] have estimated that NNES provide an additional energy delivery of 100 – 400kCal per day. According to a study by Villet et al [33] energy delivery from propofol infusion and glucose-containing IV fluids administered for sundry purposes provided as much as 150 – 600kCal/day. Similarly Hise et al [34] reported a clinically relevant amount of kilocalories (on average, approximately 250kCal/day) derived from propofol infusions and glucose-containing IV fluids in surgical ICU patients. These studies [33-34] did not take into account all of the existing inadvertent NNES, including the infusion of hydroxyethyl starches (HES), albumin solutions, immunoglobulin therapy (polygam), as well as the administration of dextrose water as part of standard ICU protocols (e.g. treatment of hyperkalemia). The extent to which these sources contribute to total energy intake is unknown and there is an urgent need for an accurate assessment of total energy delivery from both nutritional and non-nutritional energy sources to be performed in the ICU.

In conclusion, routine ICU therapeutic practices; i.e. IVFT, IV drug dilution, flushing of IV lines, as well as IV electrolyte replacement may significantly impact on total nutritional and fluid and electrolyte intake. The inappropriate administration of IV fluids is known to be a significant cause of patient morbidity and mortality.[2,4,35] Electrolyte disturbances, depending on the degree, may also have serious clinical consequences including significant impact on delivery and tolerance of NT.[8] In addition the impact of inadvertent NNES on total energy intake is of great concern since both over- and underfeeding are associated with adverse outcomes.[29-30] An accurate assessment of the contribution of NNES to total energy delivery is therefore paramount.

This study was undertaken to assess the impact of routine ICU therapeutic practices, i.e. IVFT, IV drug dilution, flushing of IV lines, IV electrolyte replacement, lipids delivered with sedatives (propofol), sucrose delivered with immunoglobulin therapy (polygam infusion), and dextrose water administered as part of standard ICU protocols on a patient's total fluid, electrolyte, energy and macronutrient intake.

CHAPTER 2
LITERATURE OVERVIEW

2.1 Intravenous (IV) fluid and volume management

2.1.1 Indications

IV fluid and volume management, also known as IVFT, is one of the most basic interventions in the ICU and plays a crucial role in achieving and maintaining fluid and electrolyte balance in critically ill patients.[10,19] The primary goal of IVFT is to achieve adequate circulating blood volume and cardiac output in order to ensure adequate tissue oxygenation for the prevention of multiple organ failure.[2,3,10,19] Furthermore it aids in the prevention of cerebral oedema in acute or chronic hyponatraemia and also plays an important role in correcting modest extracellular fluid (ECF) depletion, replacing ongoing losses, avoiding oligouria and providing maintenance fluids to replace insensible fluid and electrolyte losses (e.g. in sweat and via gastrointestinal (GI)-tract).[19] Yet according to Cannesson [20] ICU physicians face difficulty in optimising patients' fluid status on a daily basis.

2.1.2 Fluid and electrolyte imbalances in critical illness

Fluid balance can be defined as the difference between intake and output and requires consideration of the total body water (TBW), its compartmental distribution and plasma composition. The volume status of a patient is influenced by several parameters. Critical illness encompasses a wide range of physiological abnormalities that are related to impaired fluid regulation, putting the critically ill patient at high risk of fluid and electrolyte imbalances.[10]

2.1.2.1 Conservation of sodium and water and increased potassium excretion

The physiological stress response to critical illness, surgery or trauma leads to an antidiuretic effect manifesting with oliguria mediated by the release of vasopressin and catecholamines, as well as the activation of the renin-angiotensin-activating-system (RAAS). This results in water and sodium retention often in the setting of fluid overload.[2] Sodium excretion is further hampered by an increase in potassium excretion caused by the activated RAAS system. Increased nitrogen excretion due to the stress-induced catabolic state competes with that of sodium and chloride, resulting in increased water and sodium retention and worsening of interstitial oedema.[2] The reduced physiological capacity to excrete water and sodium is further aggravated by starvation.[22]

2.1.2.2 Increased capillary permeability

Sepsis or the systemic inflammatory response syndrome (SIRS) is associated with increased capillary permeability and leakage of plasma proteins, water and electrolytes from the intravascular- to the interstitial compartment.[2,10,23] The leakage of albumin into the interstitial space reduces the intravascular oncotic pressure causing a net fluid shift from the intravascular to the

interstitial compartment. This in turn leads to intravascular hypovolemia, [2,10,23] as well as pulmonary and peripheral oedema.[23] Intravascular hypovolemia also leads to further activation of the RAAS system worsening sodium retention and potassium excretion. [2]

2.1.2.3 Shedding of the endothelial glycocalyx

The endothelial glyococalyx (EG) consists of membrane-bound proteoglycans and glycoproteins found on the luminal side of the endothelium which together with bound plasma constituents, bind approximately one litre (1L) of non-circulating plasma volume. The EG plays a major role in vascular barrier function, reducing inflammation and tissue oedema [36] and is important with regard to fluid management in inflammation and in the perioperative phase.[4] However, there are certain physiological and pathophysiological processes which can lead to shedding of the glycocalyx.[4,36] These include:

- Ischaemia/reperfusion [4,36]
- Proteases [36]
- Inflammatory cytokines, such as tumour necrosis factor (TNF)-alpha [4,36] and bacterial lipopolysaccharide (LPS) [4]
- Oxidised low density lipoproteins (LDL) [36]
- Hypervolemia [3-4,36]

Under normal circumstances, water and small solutes pass through the intact glycocalyx, while colloids and proteins remain intravascularly. Flooding of the vascular system with excessive amounts of IV fluids contributes to EG shedding and increases vascular permeability, followed by plasma extravasation and interstitial oedema.[3-4] This is not merely a direct effect of the volume itself, but also due to anti-natriuretic protein (ANP)-mediated enzymatic breakdown of integral components of the EG. There is still an ongoing debate on the upper threshold for fluid administration above which extra fluid will result in glycocalyx disruption.[4,36]

2.1.2.4 Other contributing factors

Mystical third space losses

The third space essentially refers to the transcellular space consisting of endothelial lined compartments like the pleural and intraperitoneal spaces or the anterior and posterior eye chambers.[4] The third space was previously thought to be anatomically separated and not in dynamic equilibrium with the interstitial space and intravascular compartment [36] and has been divided into anatomical and non-anatomical parts. Anatomical losses were regarded as pathological fluid accumulations in the interstitial space which, together with the plasma, forms the

functional extracellular volume. On the other hand, non-anatomical losses represented what was described as the classical “third-space” fluid shift and was thought to be mainly caused by major surgery and trauma.[3,36] Examples of classical “non-anatomic” third space losses are fluid accumulation in transcellular fluid spaces, such as traumatized tissues, bowel, and peritoneal and pleural cavities, which normally contain insignificant amounts of fluid.[3] Fluid trapped into this third space was believed to be permanently lost for extracellular exchange.[3,36] Traditional perioperative fluid management therefore exceeded normal requirements to account for losses into this space and consequently to achieve hemodynamic stability.[4] An excessively positive fluid balance was considered to be unavoidable if one was to maintain the functional ECF volume.[36] It was also regarded to be essential in order to treat unmeasured fluid losses caused by a preoperative fluid deficit and insensible losses.[36] In spite of intensive research, a classic third space has not been identified.[3] According to Brettner et al,[4] bearing in mind the negative consequences of artificial hypervolemia on the EG another explanation other than “fluid shift into the third space” is required. Jacob et al [36] further suggests that the classical “third space” is most likely pure fiction and that perioperative fluid shifts consist rather of losses from the intravascular to the interstitial space, which in turn is to a large degree caused by inappropriate perioperative fluid management; i.e. infusing the wrong IV fluid in an excessive amount. Jacob et al [36] concluded that perioperative fluid shifts can be qualitatively divided into two types; namely the physiological and the pathological. The physiological (type-1) fluid shift refers to a leak of protein-free fluids across an intact barrier caused by crystalloid hypervolemia whereas the pathological (type-2) fluid shift refers to leak of protein-rich fluid related to disruption of the EG.[3,36] Avoiding hypervolemia will therefore protect the vascular barrier and minimize perioperative fluid shifts.[36]

Pre-operative fasting

According to Heckel et al [3] hypovolemia and extravascular dehydration frequently occurs as a result of pre-operative fasting, however, Brettner et al [4] point out that the impact of overnight fasting on intravascular volume is less than previously thought and is probably practically negligible. The body is able to compensate for short term fasting by recruiting fluid from the interstitial to the vascular space and the traditional practice of infusing crystalloids and colloids to compensate for an assumed intravascular deficit may actually lead to ANP-mediated shedding of the EG.[4] Although patients receiving bowel preparation prior to intestinal surgery are at risk of intravascular depletion,[4] the need for bowel preparation is controversial and most authorities feel that it is unnecessary. The ingestion of carbohydrate-rich clear fluids up to two hours prior to general anaesthesia, with re-initiation of oral fluids as soon as possible post-operatively, is now widely recommended and led to a reduction in the incidence of preoperative fluid and salt depletion.[4,37-38]

Insensible perspiration and evaporation from wounds and exposed gut

Insensible losses which include perspiration, faecal loss and evaporation from wounds and exposed gut add to fluid losses in the immediate postoperative period.[3] However, these losses are much less than previously thought and are estimated to be between 0.5ml/kg/hr in minor to 1ml/kg/hr in major abdominal surgery.[4]

Nutrition therapy (NT)

Critical illness-related fluid and electrolyte abnormalities are further influenced, purposefully or involuntary, by the provision of NT.[23]

Fluid resuscitation

Fluid resuscitation may further contribute to fluid and electrolyte imbalances and, depending on the composition of the resuscitation fluids, may lead to acid-base and electrolyte abnormalities, such as hyper- or hyponatraemia.[10] Special caution should be taken in patients at high risk of fluid and electrolyte imbalances, such as perioperative patients and those with pre-existing renal or cardiopulmonary disease.[39]

2.1.3 Complications of hypo- and hypervolemia

According to Hilton et al [35] a patient's ability to tolerate relative hypo- or hypervolemia decreases with increasing severity of acute illness.

2.1.3.1 Hypovolemia

Hypovolemia, defined as an ECF deficit, may occur as a decrease in water volume, with or without an electrolyte deficit.[40]

Hypovolemia as a water deficit alone is generally caused by an inability to regulate water intake (e.g., concentrated EN or loss of the thirst mechanism).[40] In this setting, treatment is aimed at replacing water in order to regain sodium homeostasis and restore serum osmolality to normal. IV fluid replacement should be administered as 5% dextrose in water or as a hypotonic solution in the case of hypotension.[40]

Hypovolemia, with a combined water and electrolyte deficit is caused by excessive losses (e.g., GI losses, diuretic therapy, or postoperative fluid sequestration). The sodium and volume deficit is calculated in order to determine the need for fluid and electrolyte replacement. Treatment includes; (1) treating the primary problem, (2) water restriction and (3) sodium replacement. An isotonic

solution (e.g. normal saline) is often indicated and vasopressin-receptor antagonists are used to help inhibit the action of the anti-diuretic hormone (ADH).[40]

The consequences of hypovolemia are determined by the extent of fluid lost, the timing and adequacy of volume replacement, as well as the patient's clinical context. Minor hypovolemia ranges from thirst and postural hypotension, worsening of perioperative nausea and vomiting, and the potential for prolonged hospital stay.[35] Severe acute hypovolemia clinically manifests as shock.[3,35] It leads to circulatory and tissue hypoperfusion with subsequent tissue hypoxemia, cellular dysfunction and organ injury.[3,41] This in turn increases the risk of organ failure.[3] For this reason hypovolemia is often associated with oliguria and occasionally with acute kidney injury (AKI). Furthermore it may also impair microvascular blood flow in vascular beds such as the splanchnic circulation [23] which may negatively impact on tolerance for EN. The target of volume resuscitation is therefore to maintain adequate tissue perfusion and oxygenation.[2-3,10,19]

2.1.3.2 Hypervolemia

Hypervolemia, defined as an ECF volume expansion, may occur as a result of altered renal function, plasma to interstitial fluid shift, or excessive fluid administration.[40] According to Hilton et al [35] the signs and symptoms of fluid overload are determined by the extent to which the fluid balance is positive, the severity of underlying cardio-respiratory disease, as well as the nature and severity of critical illness.

There is a strong link between crystalloid overload and the presence of pulmonary oedema, both cardiogenic in the presence of myocardial dysfunction, and as it occurs in the acute respiratory distress syndrome (ARDS), in critical illness.[10,35,41] Compared to an otherwise healthy patient, the acute physiological changes seen in critical illness and major surgery (primarily the capillary leak as described above) decrease the ability to tolerate excessive infusion of crystalloids, putting the patient at risk of symptomatic respiratory failure.[35] Crystalloid overload is also associated with cerebral oedema in patients with concomitant head injury, abdominal compartment syndrome (ACS), and peripheral and gut oedema.[10,23]

Postoperative fluid overload is associated with a range of serious complications. Soft tissue oedema decreases lymphatic drainage and local oxygenation, leading to tissue hypoxemia and delayed wound and anastomotic healing. Gut oedema may result in EN intolerance, translocation of endotoxin or bacteria, with potentially detrimental consequences such as sepsis and multi-organ failure. It may also result in prolonged post-operative ileus. Furthermore, crystalloid infusion may augment coagulation increasing the risk of postoperative thrombosis.[41]

Treatment of hypervolemia includes the restriction of fluid and/or sodium with or without the use of diuretics. Biochemical abnormalities associated with hypervolemia often include hyponatremia and

hypo-osmolality and may require sodium restriction to prevent further worsening of fluid retention. Patients who are hypervolemic and hyponatraemic require free water- and sodium restriction and in some cases the use of diuretics to achieve effective fluid mobilization.[40]

2.1.4 Solutions available for IV fluid therapy (IVFT)

Table 2-1 indicates the most commonly used IV fluids for IVFT; namely crystalloids, colloids and blood products. For the purposes of this study the composition of blood products will not be discussed.

Table 2-1 Commonly used intravenous (IV) fluids [3]

Crystalloids	Colloids		Blood products
	Natural	Artificial	
Glucose solutions	Albumin	Gelatin	Whole blood
Sodium chloride solutions		Dextran	Erythrocyte concentrate
Electrolyte solutions, balanced		HES 130	Fresh frozen plasma
Electrolyte solutions, unbalanced		HES 200	
Abbreviations: HES: Hydroxyethyl starch			

2.1.4.1 Crystalloids

Crystalloid solutions consist of small, water-soluble molecules that can easily move across the intact vascular barrier into the interstitial space.[2,4] The main solute is either sodium chloride (saline) or glucose.[37] Crystalloids can be isotonic, hypotonic, or hypertonic with respect to plasma.[37] Table 2-2 gives a breakdown of the commonly used crystalloid solutions.

Isotonic crystalloids have an osmolarity equal or close to that of human plasma (280 – 300 mOsm/L). Isotonic crystalloids can either have a “normal” sodium concentration, i.e. a sodium concentration nearer to that of human plasma (136 – 145mmol/L), such as sodium chloride 0.9%

("normal" saline) and Hartmann's solution or a "low" sodium content such as sodium chloride 0.18%/glucose 4% or glucose 5%. Fluids with "normal" sodium content freely move within the ECF compartment causing little alteration in sodium concentration and osmolarity. This restricts the movement of water out of the ECF into the intracellular fluid (ICF) compartment and vice versa.[2] 'Normal' saline contains more chloride than the ECF and inappropriate administration may lead to hyperchloraemic acidosis.[2,4] Balanced crystalloids, e.g. Hartmann's solution, have ion concentrations and tonicity nearer to that of human plasma and are more "physiological" and do not cause hyperchloraemic acidosis.[4] Isotonic crystalloids with low sodium content are ideal for rehydration since they freely move between the ICF and ECF compartments once the glucose component has been metabolised. Excess administration may however result in hyponatremia.[2]

Non-isotonic crystalloids can either be hypo- or hypertonic and are normally reserved for special conditions where manipulation of plasma osmolarity is needed.[2] Hypertonic formulations may offer potential benefit with regard to the formation of tissue oedema, fluid balance, and intracranial or ACS.[23] Mannitol is currently the first-line drug for osmotherapy in intracranial hypertension, but hypertonic saline can be added as an adjunctive treatment modality in cases where raised intracranial pressures are not adequately controlled by mannitol.[23] It causes an increase in the ECF sodium concentration resulting in a net fluid shift from the ICF to the ECF, hence reducing cerebral oedema.[2]

Table 2-2 Composition of commonly used crystalloid solutions (per litre) [2,38,42]

Crystalloid Solution	Na	K	Cl	Ca/ Mg	Lactate (g/L)	HCO_3 (g/L)	Osmolarity (mOsm/L)	pH	Dextrose (g/L)	Energy kJ/L
Saline 0.9%/ Normal saline	154	-	154	-	-	-	308	5.5	-	-
Hartmann's/ Ringer Lactate	131	5	111	Ca 1.8	29	-	275	6.0	-	-
Modified Ringer Lactate	131	5.4	108	-	29	-	273	6.0	-	-
Balsol	130	4	110	Mg 1.5	-	27	273	7.4	-	-
Dextrose 5%	-	-	-	-	-	-	278	4.5	50	840
Saline 0.45%	77	-	77	-	-	-	154	5.5	-	-
Dextrose 5% in saline 0.45%	77	-	77	-	-	-	432	4.0	50	840
Dextrose 4% in saline 0.18%	30	-	30	-	-	-	154	4.0-5.0	40	680
Bicarbonate -8.4%	1000	-	-	-	-	1000	-	8.0	-	-
Bicarbonate -1.26%	150	-	-	-	-	150	-	7.0	-	-

Units are in mmol/litre unless otherwise stated.

Abbreviations: Na: Sodium; K: Potassium; Cl: Chloride; Ca: Calcium; Mg: Magnesium; HCO_3:Hydrogen carbonate

2.1.4.2 Colloids

Colloids are composed of larger, more insoluble molecules that do not readily cross semipermeable membranes.[2] Colloids are either semi-synthetic (e.g. gelatins, dextrans, and HES) or naturally occurring human plasma derivatives (e.g. human albumin solutions, plasma protein fraction, fresh frozen plasma, and immunoglobulin solution).[3] Movement of colloid out of the intravascular space is determined by the molecular weight (MW), shape, ionic charge of the constituents and capillary permeability.[2] Whereas most colloids are suspended in 0.9% sodium chloride solutions, several balanced colloid solutions are now available.[2] Table 2-3 gives a breakdown of commonly used colloid solutions.

Albumin is the only natural colloid used clinically.[2-3] It is derived from human plasma by fractionation. Under normal physiologic conditions, albumin is the primary determinant of the intravascular osmotic pressure. It is therefore seen as an ideal colloid to restore protein losses from the vasculature.[3] Albumin solutions are available as 4.5%, 5% or 20% solutions.[2] Despite albumin's low vascular permeability in the healthy patient due to its negative charge, losses occur in critical illness as a result of the capillary leak associated with inflammation.[2] Over the past decade there has been considerable debate over the use of albumin in critically ill patients.[2] It has been linked to severe allergic reactions and immunologic complications and has previously been shown to worsen outcomes in patients with traumatic brain injury (TBI).[3,43] However, Marsh and Brown [2] point out that the Saline versus Albumin Fluid Evaluation (SAFE) study by Finfer et al (2004) found no association between albumin infusion and increased mortality in critically ill patients as a group.

Gelatins are polydispersed polypeptides synthesized from the degradation of bovine collagen and therefore carry the risk of anaphylaxis.[2,3] According to Heckel et al [3] all gelatin preparations are considered safe with regard to organ function and coagulation. However, there is still considerable debate regarding the effect of gelatins on renal function.

Dextrans are colloids made with large glucose polymer molecules. They are rarely used due to potential side effects including osmotic diuresis, abnormal platelet function, renal failure, coagulopathy and interference with blood cross-matching.[2]

Hydroxy-ethyl starches (HES) are artificial polymers derived from amylopectin, a highly branched chain of amylopectin (glucose) molecules obtained from waxy maize or potatoes, linked with hydroxyl-ethyl groups making the resultant polymer similar to glycogen.[2,3] Negative effects of high molecular HES on the coagulation system have been reported. Preparations above 200kDa cause a reduction in *von Willebrand factor* and factor VIII, leading to decreased platelet adhesion. [2] HES colloids have also been linked to serious adverse events, such as hemostasis due to platelet

coating [4] and to particularly impaired renal function.[2,4] According to Heckel et al [3] the most probable link between colloid infusion and impaired renal function is the potential to increase urine viscosity from the infusion of hyperoncotic colloids in dehydrated patients. These adverse effects on renal function and coagulation are not as conspicuous with the use of low molecular weight (LMW) HES (e.g. 6% 130/0.4) compared to the older high molecular weight starches.[2-4] Nevertheless, the use of HES IV fluids in ICU remains controversial and even more so after the publication of recent trials and review articles.[44-50] Further research should therefore be undertaken to clarify the extent to which HES IV fluids may be associated with adverse events, particularly impaired renal function.[2]

Table 2-3 Composition of commonly used colloids (per litre) [2,42]

Colloid Solution	Na	K	Cl	Ca	Mg	Other (g/L)	Osmolarity (mOsm/L)	pH	Energy (kJ/L)
A: Gelatins									
Gelofusine MW 30 000	154	0.4	125	0.4	0.4	Gelatin 40g	290	7.4	-
Haemacel MW 30 000	145	5.1	145	6.25	-	Gelatin 35g	301	7.3	-
B: Dextrans									
Dextran 70 in dextrose 5% MW 70 000	-	-	-	-	-	Dextran/ Dextrose: 60g/50g	287	5 – 6	1841
Dextran 70 in saline 0.9% MW 70 000	154	-	154	-	-	Dextran 60g	287	4 – 5	1004
C: Hydroxyethyl starches (HES)									
Hespan 6% MW 200 000	154	-	154	-	-	Starch 60g	310	5.5	1020
Voluven HES 6% (130/0.4) MW 130 000	154	-	154	-	-	Starch 60g	308	5.5	1004
Voluven Balanced	137	4	110	-	1.5	-	286.5	6.5	1004
Voluvyte HES 6% (130/0.4)	137	4	110	-	-	Starch 60g	286	-	1004
HES 10% (200/0.5)	154	-	154	-	-	Starch 100g	308	-	1674
HES 6% (450/0.6)	154	-	154	-	-	Starch 60g	308	-	1004
D: Human albumin solutions (HAS)									
HAS 4.5%	100-160	<2	100 - 160	-	-	Albumin/ Citrate: 45g/<15g	270 – 300	6.4-7.4	753
HAS 5%	150	-	150	-	-	Albumin 50g	300	-	837
HAS 20%	50–120	<10	<40	-	-	Albumin 200g	135-138	6.4-7.4	3348

Units are in mmol/litre unless otherwise stated.

Abbreviations: Na: Sodium; K: Potassium; Cl: Chloride; Ca: Calcium; Mg: Magnesium

2.1.5 Available intravenous (IV) fluid regimens

IVFT can be divided into two basic strategies, i.e. 1) fixed fluid replacement regimens; and 2) variable, algorithmic approaches.[35]

2.1.5.1 Fixed fluid replacement regimens

Fixed fluid regimens are most commonly used in clinical settings. It is adjusted according to individualised assessment of fluid losses and can be subdivided into the following three categories:

1. **Standard perioperative fixed fluid replacement regimens.** This usually advocates 3 litres per day of fluid of varying composition. These are often associated with fluid overload and the complications mentioned above. Hilton et al [35] therefore suggests substituting the “fixed 3 L per day” prescription for maintenance fluid requirements with a more restrictive approach, unless clearly indicated otherwise.
2. **Restrictive fluid regimens.** This is commonly used for postoperative management of pneumonectomy and lobectomy, and more recently for bowel surgery. [35]
3. **Liberal acute fluid resuscitation.** This is used to correct severe acute hypovolemia, e.g. burns.[35]

2.1.5.2 Algorithmic approaches

Algorithmic approaches to volume replacement are mostly restricted to critically ill patients in ICUs. These regimens target specific circulatory parameters and may improve patient outcomes. Targets previously included invasive monitoring of cardiac chamber filling pressures with central venous pressure (CVP) and pulmonary artery wedge pressure and today more frequently use noninvasive techniques such as measurement of stroke volume variation and measurement of cardiac output (CO) by pulse contour analysis.[35] According to Marsh and Brown [2] there is an increasing body of evidence supporting the use of CO monitoring to guide fluid therapy and that such “goal-directed” fluid therapy may have significant benefits. According to Cannesson [20] dynamic parameters of fluid responsiveness, based on cardiopulmonary interactions in patients under general anaesthesia and mechanical ventilation, are superior to static indicators (e.g. CVP). The concept of fluid responsiveness refers to the ability of the circulation to increase CO in response to volume expansion. These dynamic parameters can be obtained from a single arterial pressure waveform (systolic pressure variations (SPVs) and pulse-pressure variations (PPVs)). It allows for optimization of the dynamic indicators of fluid responsiveness and offers an alternative to CO monitoring and optimization. According to recent studies this approach has the ability to improve postoperative outcomes. However, dynamic parameters of fluid responsiveness can only be used

in mechanically ventilated patients under general anaesthesia. It also requires a tidal volume of 8 mL/kg of body weight with a positive end-expiratory pressure between 0 and 5cmH2O to be able to use these indices. If unable to use these indices, alternative dynamic parameters can be used, such as echocardiography, passive leg raising to determine its effect on stroke volume and assessing preload dependence. Further studies are required to better define how these parameters can be implemented in clinical protocols for perioperative fluid management.[20]

2.1.6 The use of crystalloids versus colloids in the treatment of acute hypovolemia and dehydration

Considerable debate revolves around matters such as the use of crystalloids versus colloids in the treatment of acute intravascular hypovolemia and extravascular dehydration. According to Marsh and Brown [2] any IV fluid should be seen as a drug with potential benefits and side effects. No single IV fluid has the ability to offer appropriate fluid and electrolyte components on its own. Crystalloids and colloids should therefore be seen as two separate classes of IV fluids and that each has its own unique part to play in terms of fluid management.[20] The type of IV fluid administered should always reflect the given patient's volume and electrolyte status, as well as the clinical goal at hand.[2] Firstly it is important to differentiate between dehydration of the extravascular compartment and acute intravascular hypovolemia, since the type of fluid used in the treatment of each differs.[3]

Dehydration of the extravascular compartment is caused by fasting, urine production and insensible losses resulting in a loss of electrolytes and colloid-free fluid initially from the interstitial space. Only thereafter does it influence the intravascular compartment. In this setting dehydration should be treated by refilling the interstitial space and replacing additional losses by crystalloid infusions. In practice, since only the intravascular compartment is directly accessible, balanced crystalloids which freely distribute between the interstitial and intravascular compartments are suitable for this purpose.[3] According to Heckel et al [3] treating extravascular dehydration with colloids in a normovolemic patient may result in iatrogenic hypervolemia and subsequent glycocalyx damage and tissue edema.

On the other hand, acute intravascular hypovolemia primarily affects the intravascular compartment and is therefore potentially life-threatening.[3] There is ongoing debate regarding the use of crystalloids (isotonic) versus colloids (roughly iso-oncotic) for the treatment of hypovolemia and shock.[51] Large clinical trials and systematic reviews suggest no superiority of one over the other with regard to effects on overall mortality. However, it is important to consider the heterogeneity of critically ill patients and that the effects on hemodynamics, adverse effects and outcomes may differ among different patient populations.[51]

According to Bauer et al [23] isotonic crystalloids are probably superior to artificial colloids in the septic patient. Crystalloids are cheap, easily available and have a low risk of anaphylaxis, but on the other hand are less effective than colloids at refilling the intravascular compartment.[2,51] According to Heckel et al [3] only one fifth of the intravenously infused crystalloid solution remains in the intravascular compartment and should therefore not be used for volume resuscitation in acute hypovolemia. Treating hypovolemia with crystalloids may result in persistent hypovolemia with a concomitant reduction in intravascular oncotic pressure leading to the formation of interstitial edema.[3,51] Table 2-4 indicates the proposed colloid to crystalloid volume ratios as published by several authors.

Table 2-4 Colloid to crystalloid volume ratio

Proposed volume ratio (colloid to crystalloid)	Reference
1 : 3	Trof and Groeneveld (2011) [51]
1: 4	Heckel et al (2011) [3]
1 : 1.5	Bauer et al (2009) [23]

As a consequence various authors recommend the use of colloids for the treatment of acute hypovolemia, since they remain essentially within the intravascular space and maintain oncotic pressure.[2-4,51] It is however debatable whether the theory behind colloid use for the management of acute hypovolemia applies to critically ill septic patients who suffer from capillary leak and impaired glycocalyx barrier function. One could assume that a severely impaired vascular barrier will result in both colloids and crystalloids being able to distribute freely across the vascular barrier. It is questionable however whether this finding can be generalized to every critically ill patient. There is unfortunately no bedside parameter for measuring vascular barrier function.[3] There is a currently a large amount of research being performed on albumin and starch molecules in the management of hypovolemia in patients presenting with hyperinflammatory conditions.[51] According to Trof and Groeneveld [51] the electrostatic properties of albumin enable it to penetrate and bind to the overlying luminal glycocalyx. This subsequent “sealing effect” may decrease fluid movement into the interstitium independently of the colloid oncotic pressure by albumin.[51] The benefits of albumin infusion may however be patient specific. Albumin may offer benefit to those presenting with hypoalbuminemia (e.g. sepsis, ALI) but may worsen outcome in patients with TBI.[43] TBI patients may therefore rather benefit from the use of iso-and/or hypertonic saline.[23]

Large HES molecules have also been claimed to have a similar “sealing” effect, but the clinical significance is uncertain if it occurs at all. In animal experiments and clinical studies, the use of 6% HES 130/0.4 lead to a reduction in typical perioperative complications, e.g. wound infection, pneumonia and anastomotic leak, and improved bowel tissue oxygenation and microcirculatory blood flow.[3] On the other hand a number of recent trials and reviews showed an association

between the use of HES and impaired renal function [44-46,50] and led to international regulatory bodies issuing recent statements that HES IV fluids should be withdrawn from clinical use; (2) its clinical use reviewed; or (3) used with extreme caution in ICU, cardiac surgery and patients with known kidney disease or coagulopathy.[52-54] Based on these recommendations the Western Cape Department of Health withdrew all IV fluids containing HES from hospitals in the Western Cape,[55] with similar action contemplated in the Free State and Gauteng. Of great concern, however, is that the recommendations have been based on flawed scientific evidence and applied to clinical settings not included in the studies. In these studies HES were mostly administered to critically ill patients with sepsis,[44-46,50] outdated hyperoncotic HES solutions were used [44,50] and were administered in excessive amounts over prolonged periods of time.[4,50] Furthermore the use of HES in patients with trauma or those undergoing major elective or emergency surgery for non-septic disease were not addressed by these studies. According to a randomised controlled trial (RCT) [47] comparing HES with 0.9% saline in trauma patients, renal injury occurred more frequently in the saline group than the HES group (16% vs. 0%; P = 0.018). A recent meta-analysis has also demonstrated the efficacy of colloid solutions, including HES, as a fluid replacement agent during caesarean sections.[48] The Enhanced Recovery After Surgery (ERAS) program for major elective surgery, such as colectomy, also support the use of colloids such as HES for replacement of intraoperative blood loss in preference to crystalloids.[49] On the contrary two recent studies published in 2012, the 6S study [45] from Scandinavia and the CHEST study from Australia,[46] found HES to be associated with an increased risk of renal replacement therapy (RRT) particularly in elderly, critically ill septic patients.

Based on these two trials the conclusion can be drawn that HES should be avoided in elderly, critically ill patients with sepsis.[45,46] On the other hand there seems to be no evidence that HES should be avoided in non-septic patients without critical illness who require intravascular volume replacement, but not transfusion. Until stronger evidence is available the prescription of these fluids is likely to be based on personal choice and clinical indication.[2]

2.2 Management of electrolyte disturbances

Critically ill patients often present with electrolyte and metabolic disturbances.[56] Depending on the degree, electrolyte disturbances may have serious clinical manifestations and require urgent replacement or removal with measures specific to the abnormality. In most ICUs abnormal values are generally corrected by the patient's physician during rounds. However, this practice lacks standardization and the dosing, timing and monitoring of electrolyte replacement varies considerably from clinician to clinician. The implementation of multi-disciplinary electrolyte replacement protocols may therefore improve overall electrolyte replacement and its effectiveness.[8] Important to consider is that the use of replacement fluids in the management of

electrolyte disturbances provide volume and potentially nutrients. For example, (1) hypernatremia is often treated by the administration of free water in the form of 5% dextrose water; [57] and (2) hyperkalemia is often treated by a concomitant administration of dextrose with insulin.[40]

2.3 Dilution of IV medications and -supplements

IV medication administration refers to the infusion of medication directly into a patient's vein. The main purpose of giving IV medication is to initiate a quick systemic response to medication. IV medication can be administered as a bolus ("push-in"), intermittently or continuously.[7] "Push-in" drugs are usually diluted in 10ml of sterile water unless otherwise stated and given through a freely running IV line over a period of not less than three minutes. Drugs administered intermittently or continuously require specific dilution or are pre-diluted by the manufacturer and require specific infusion time.[58] Furthermore the IV tubing or cannula should be flushed with saline before and after drug administration.[7]

The volume and composition of the IV solutions used for IV drug dilution and flushing of IV lines contribute to total fluid, electrolyte and potentially energy intake. Many studies assessing energy intake among ICU patients did not account for the use of dextrose containing IV fluids in the dilution of IV drugs, for example in hypernatraemic patients.

2.4 Link between nutrition and fluid and electrolyte balance

Nutrition and fluid and electrolyte balance are closely linked through ingestion, digestion, absorption and intermediary metabolism.[21,22] The intake of food by natural or artificial means cannot be separated from that of fluid and electrolytes.[21,25] Furthermore, the physiological processes of digestion and nutrient absorption in the small and large intestines are closely linked to the secretion and absorption of water and electrolytes. Lastly, fluid and electrolytes play a crucial role in intermediary metabolism and cellular function. In clinical practice nutrient, water, mineral and electrolyte balance are closely related in the treatment of disease. [21]

2.4.1 Enteral nutrition (EN)

Fluid and electrolyte balance influences GI function and subsequent tolerance of EN.[22] Published evidence suggests that fluid overload delays gastric emptying and intestinal transit, prolongs post-operative ileus and delays feeding via the enteral route.[21,22,25] According to Allison [22] even a moderate saline overload may result in prolonged post-operative ileus. Furthermore, clearance of oedema (via salt restriction and diuretics) appears to be coupled with a return in GI function, allowing nutrition via the oral or enteral route.[21,22] Lobo hypothesizes that fluid and electrolyte

balance, and not the serum albumin concentration per se, is the primary determinant of recovery from post-operative ileus.[21] There is a close relationship between serum albumin concentration, illness, nutrition and fluid balance.[22] Avoidance of fluid and sodium overload, reduced fasting times pre- and postoperatively, pre-operative carbohydrate loading and early initiation of post-operative EN all form part of the ERAS guidelines on reducing the stress induced by surgery and facilitate the return of GI function [26] and subsequent EN tolerance.

According to Lobo [21] a study by Wilkes et al (2001) found that hyperchloraemic acidosis caused by excessive saline infusions reduces gastric blood flow and decreases gastric intra-mucosal pH in elderly surgical patients. Fluid overload may also result in splanchnic or gut oedema.[21,22] Splanchnic oedema may lead to increased abdominal pressure, ascites, and ACS. This in turn causes a reduction in mesenteric blood flow and increases the risk for complications, such as ileus (acute intestinal failure) with subsequent intolerance of EN, functional obstruction of anastomoses, increased gut permeability, intestinal failure and anastomotic dehiscence.[21,22] Potassium supplementation may play a beneficial role in the prevention of post-operative ileus. Therefore routine IV potassium supplementation starting from theatre is recommended and regarded safe.[39] Figure 2-1 illustrates the possible link between fluid overload an impaired GI function.

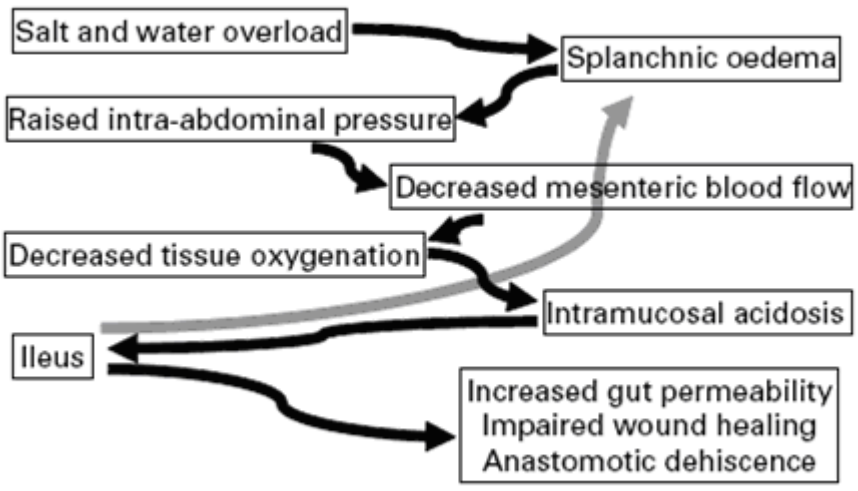

Figure 2-1 Hypothesis for the effects of salt and fluid overload on GI function [21]

On the other hand, severe fluid and electrolyte abnormalities may develop as a result of existing intestinal failure, e.g. short bowel syndrome. These fluid and electrolyte abnormalities can be life threatening in the case of inappropriate or delayed treatment. Treatment should be based on a multidisciplinary assessment of the underlying disease process, fluid status, absorptive capacity of the GI tract and renal function involving the attending physician, nurse, dietician and pharmacist.[40] The electrolyte concentration of most EN products are based on the assumption that the patient's

macronutrient requirements will be met using that feed, e.g., 2000 ml/day. If a patient is unable to tolerate adequate EN, the intake of electrolytes will be similarly reduced and inadequate. Furthermore, intestinal absorption of minerals (especially calcium, magnesium and phosphate) is often compromised. It can therefore be challenging to restore electrolyte deficiencies in patients with pre-existing deficiencies (e.g., electrolyte deficiencies caused by sepsis, trauma or previous malnutrition), increased extra-renal losses and high output fistulas or stomas, by the enteral route alone. These conditions may require additional enteral or IV fluid and electrolyte administration.[25]

2.4.2 Parenteral nutrition (PN)

It is essential to determine the exact fluid and electrolyte requirements when prescribing PN for critically ill patients, especially for those with fluid and electrolyte imbalances in the presence of shock, sepsis and renal insufficiency. This necessitates daily monitoring of fluid and electrolyte status and also requires a multidisciplinary approach, especially if teams are mutually exclusive. Prompt treatment of the underlying condition responsible for the fluid imbalance is paramount. The symptoms of fluid imbalance can be managed by means of individually adapted PN, for e.g., in critically ill patients with renal failure or chronic renal, lung, heart or liver insufficiency. Fluid and electrolyte intake via all routes, as well as additional losses (e.g. diarrhoea) should be strictly monitored and appropriate changes in fluid and electrolyte intake made in patients who are at risk. Intake should be individually determined when electrolyte balance is acutely altered (e.g. due to chronic diarrhoea, recurring vomiting, renal insufficiency, etc.). Many commercially available multi-chamber bags and amino acid solutions contain electrolytes in various doses, which may not always meet the long-term PN patient's requirements. It is important to take these quantities into account when determining electrolyte intake and when calculating additional needs.[24]

2.4.3 Monitoring fluid and electrolyte status in patients receiving nutrition therapy (NT)

Achieving and maintaining fluid and electrolyte balance plays a crucial role in obtaining the full benefit from NT.[22] Calculation of fluid and electrolyte requirements is as important as determining a patient's macro- and micronutrient needs when prescribing NT.[21,25] Daily monitoring of fluid and electrolyte status should therefore be incorporated into the dietician's daily ICU round to ensure successful management of fluid and electrolyte balance in patients receiving NT.[25] Assessing input and output charts provide valuable information on fluid status,[25] however, frequent errors in the measurement and recording of fluid input and output, e.g. urine output and GI losses, combined with neglect of insensible losses, often results in a large cumulative error in fluid balance. Monitoring of charts should therefore be combined with other indicators of fluid balance to obtain a more accurate reflection of a patient's fluid status. For example, combining input and output charts with daily weighing will give a better indication of changes in fluid balance[25-26] However, ICU

patients are mostly bedridden and seldom weighed.[59] Even with the use of electronic bed scales, Schneider et al [59] found that obtaining daily body weights were difficult and that compliance was poor. Daily evaluation for evidence of dehydration, oedema or ileus, combined with daily monitoring of changes in urea, creatinine, sodium, potassium, magnesium, calcium and phosphate is recommended and will assist in adjusting the volume or electrolyte content of NT appropriately.[25-26]

2.5 Fluid, electrolyte, energy and macronutrient requirements of the critically ill patient

2.5.1 Fluid and electrolyte requirements

Table 2-5 indicates the normal daily fluid and electrolyte requirements during maintenance of NT in critically ill and/or perioperative patients as recommended by various authors. The electrolyte recommendations serve as a general guideline for patients with normal renal and liver function and for those with normal serum electrolyte concentrations.[38] Electrolyte intake frequently requires adjustment during maintenance NT based on the clinical condition [25] and additional replacement may be required during the acute resuscitation of a hypovolemic patient.[21] Table 2-6 shows examples of conditions that frequently require electrolyte adjustment.

Table 2-5 Maintenance fluid and electrolyte requirements of critically ill patients requiring NT

		Allison 2004 [22]	Lobo 2004 [21]	Rassam 2005 [39]	Madsen 2006 [13]		Shields 2008 [41 (A)]	Powel-Tuck 2008 [38]	Sobotka 2009 [25]		Biesalski 2009 [24 (B)]	Mer M 2012 [42]	Marsh 2012 [2]
					EN	PN			EN	PN			
Fluid*	mL/kg/d	30–40 +10ml/kg/1˚C >37 ˚C	25–35	35	-	-	25–35	-	-	-	-	35 (18–60 yr) 30 (>60 yr) + 2 – 2.5 ml/kg/1˚C >37 ˚C	-
	L/d	-	2 – 2.5	2.5 – 3	-	-	≤ 5 (median 3)	1.5 – 2.5	-	-	-	-	-
	mL/kg/hr	-	-	-	-	-	-	-	-	-	-	1.5	1.5
Na	mmol/kg/d	-	1–1.2	2	-	-	1	-	-	-	-	-	1 - 1.5
	mmol/d	-	60–100	-	0–200	100–150	242 (median)	50-100	80 -100	80 -100	60 – 150	100	-
K	mmol/kg/d	-	1–1.2	1	-	-	-	-	-	-	-	-	1
	mmol/d	-	-	-	0–240	60–120	-	40–80 [C]	60 – 150	60 – 150	40 – 100	75	-
Cl	mmol/kg/d	-	-	-	As needed to maintain acid-base balance		-	-	-	-	-	-	1.5
	mmol/d	-	-	-			-	-	-	-	-	120	-
P	mmol/kg/d	-	-	-	-	-	-	-	-	-	-	-	0.2 - 0.5
	mmol/d	-	-	-	0 – 60	15 – 30	-	-	15 – 30	20 – 40	10–30	-	-
Mg	mmol/kg/d	-	-	-	-	-	-	-					0.1 - 0.2
	mmol/d	-	-	-	0 – 48	8 – 24	-	-	8 – 12	10 – 18	4 – 12	8	
Ca	mmol/kg/d	-	-	-	-	-	-	-	-	-	-	-	0.1 - 0.2
	mmol/d	-	-	-	0 – 25	9 – 22	-	-	2.5 – 5	25 – 50	2.5 – 7.5	-	-

[A] Postoperative guidelines; [B] Standard daily dose in PN. Additional amounts should only be given to correct deficits or ongoing losses; [C] Unless kidney disease or hyperkalemia

Table 2-6 Conditions requiring adjustment of normal electrolyte requirements[25]

Fluid/electrolyte abnormality	Condition
Fluid and Na deficiency	**Extra-renal fluid losses:** GI fistulas; Water and electrolyte losses from gastric aspiration; Severe diarrhoea; Toxic megacolon; Ileus with pooling in the gut; Short bowel syndrome; Increased skin losses (sweat) during febrile episodes or in a hot environment; Severe burns
	Increased renal losses: Polyuric renal failure (tubular impairment)
	Fluid and sodium sequestration into extracellular or transcellular compartment: Severe acute pancreatitis; Severe trauma and sepsis; Sequestration of fluid in intestine
Fluid and sodium restriction	Oliguric renal failure; Cardiac failure; Oedema in the post-acute phase of injury
K, Mg and P deficiency	Convalescence phase after trauma, sepsis or severe injury; Severe malnutrition with risk of refeeding syndrome; Severe losses of extracellular fluid (GI tract, burns); Treatment with diuretics
K, Mg, P restriction	Oliguric renal failure; Acute catabolic situations (e.g. sepsis) particularly if combined with renal failure
Abbreviations: Na: Sodium; K: Potassium; Mg: Magnesium; P: Phosphate	

2.5.2 Energy and macronutrient requirements

Despite numerous observational studies, small randomized trials, systematic reviews and consensus guidelines on NT in critical illness, many issues remain controversial; including the most appropriate substrates to use, the optimal time to initiate NT, the ideal method for assessing energy requirements and optimal nutritional targets.

Accurate determination of energy requirements in the critically ill is difficult. Firstly, resting energy expenditure is highly variable during the course of critical illness due to changes induced by shock, fever, sedation, surgical procedures and loss of lean body mass (LBM).[29,60] Secondly, accurate determination of energy targets requires knowledge of pre-illness weight and body height, data which is often missing. Thirdly, actual body weight is frequently inaccurate due to fluid

accumulation post resuscitation,[29,60] while dry body weight is a poor indicator of LBM, especially in the obese patient where body weight is increased by excess fat mass.[29]

Currently, the gold standard for predicting energy requirements is by means of measuring energy expenditure on an individual basis by indirect calorimetry.[28-29,60-62] However, this method is fairly expensive, time-consuming and remains unavailable in most ICUs.[29,62] Predictive equations are therefore frequently used as surrogates to estimate energy requirements.[28-29,62] Most of these were developed for use in the healthy population and there is currently no consensus as to the most accurate equation for estimating energy requirements in the critically ill.[28] The Harris & Benedict equation (adjusted or not for ideal body weight), and the equations of Mifflin, Owen, the American College of Chest Physicians (ACCP), Ireton-Jones 1992 and 1997, Penn State 1998 and 2003, and Swinamer 1990 are the most commonly used. However, the results from these correlate poorly with those of indirect calorimetry.[29] The most significant source of error in these equations is the use of estimated, rather than measured weight.[28] Berger and Pichard [29] suggest that the Toronto equation for major burns and the Faisy-Fagon equation for patients on mechanical ventilation were developed specifically for critically ill patients and are clinically more accurate than other predictive equations for metabolically stable, mechanically ventilated patients.[29] The last method for determining energy requirements is the use of a fixed daily prescription, usually in the range of 20 – 35 kCal/kg.[28,62] Despite the greater ease of applying this method at the patient's bedside, accuracy is generally regarded as poor. Accuracy might be improved by using metabolically active weight, instead of actual weight, but currently there is no reliable definition of metabolically active weight.[28] A number of professional organizations and authors have developed consensus guidelines for the determination of nutritional requirements in critical illness (Table 2-7).

Table 2-7 Published guidelines for nutrient intake in critically ill patients

Society	Year	Energy kCal/kg/day	Protein g/kg/day	Carbohydrates g/kg/day	Lipid g/kg/day
ACCP [63]	1997	25	-	-	-
CCCPG [64]	2003	No recommendation (insufficient evidence)	-	-	-
ESPEN [65-66]	2006	Enteral nutrition: Acute phase: 20 – 25 (Grade C) Recovery phase: 25 – 30 (Grade C) Malnutrition: 25 – 30 (Grade C)	-	-	-
	2009	Parenteral nutrition: 25 if IC not available (Grade C)	1.3 – 1.5 (+ 0.3 – 0.6 alanyl-glutamine dipeptide)	Minimum: 2	0.7 – 1.5 over 12 – 24 hours
ASPEN [67]	2009	25 or predictive equations if IC not available	1.2 – 2.0 (BMI<30kg/m2) Increase in burns and polytrauma.	-	-

Abbreviations: ACCP: American College of Chest Physicians; CCCPG: Canadian Critical Care Practice Guidelines; ESPEN: European Society of Parenteral and Enteral Nutrition; ASPEN: American Society of Parenteral and Enteral Nutrition; IC: Indirect calorimetry.

Evidence grades: B, supported by at least one well-designed randomized controlled trial or other with sound methodology; C, based on expert opinion or advice.[65-66]

2.5.3 Hypo- versus hypercaloric feeding

Considerable debate revolves around the optimal quantity of nutrition (energy and protein) that should be provided to critically ill patients in relation to clinical outcomes.[34,68] According to Berger and Pichard [29] the recent publication of studies with apparently conflicting results regarding the respective merits of hypo- and hypercaloric feeding has caused further confusion among ICU specialists. There is a general consensus that both over- and underfeeding have well defined adverse effects and should be avoided.[29,60,68] Feeding strategies suggesting that permissive underfeeding may be adequate are based on several studies that found that suboptimal provision

of calories actually improves patient outcomes compared to goal directed feeding. Table 2-8 shows a breakdown of some of the landmark studies in favour of permissive underfeeding.

Table 2-8 Landmark studies in favour of permissive underfeeding

Study reference	Study design	Level of caloric intake	Results
Krishnan 2003 [69]	Observational	33 – 65% of ACCP target (9-18kCal/kg)	Improved survival
Hise 2007 [34]	Observational	< 81% of energy target	Shorter ICU and hospital LOS
Arabi 2011 [70]	RCT	Permissive underfeeding versus target feeding (59% vs 71%)	Lower hospital mortality in permissive underfeeding group
Rice 2012 [71]	RCT	Trophic feeding versus target feeding during first 6 days in ALI patients	No difference in clinical outcomes More GIT disturbances in target feeding group
Abbreviations: ACCP: American College of Chest Physicians; RCT: Randomized controlled trial; ICU: Intensive care unit; LOS: Length of stay; ALI: Acute lung injury; GIT: Gastrointestinal			

However, most of these studies did not take into account the additional calories derived from NNES (i.e. dextrose-containing IV solutions or lipid-based sedatives), thus limiting the conclusions made regarding energy goals for critically ill patients.[28] In addition the controls fed according to traditional protocols [70-71] did not receive sufficient protein which is perhaps more important than calories alone.[72] Dickerson [30] recommends further research to determine the minimum amount of nutrition (calories and protein) needed to achieve a therapeutic benefit and to determine at what intake no further benefit accrues. According to Peake et al [28] short periods of hypocaloric feeding are considered a normal response to acute illness, usually involving anorexia and reduced intake, and might not negatively impact clinical outcomes. It is also possible that some variation in calories within a defined range, delivered over a variable time frame, might not influence clinical outcomes. However, prolonged underfeeding may result in a cumulative energy/protein debt that cannot be compensated for later during ICU stay due to complications related to overfeeding.[28,33] Hence, at some point in time cumulative malnutrition and loss of muscle mass will influence recovery.[28] Table 2-9 is a summary of previous studies reporting that underfeeding has a negative impact on clinical outcomes.

Table 2-9 Studies reporting negative impact of underfeeding on clinical outcomes

Study reference	Study design	Level of calorie intake	Results
Rubinson 2004 [73]	Observational	< 25 % of energy target	Increased risk of blood stream infections
Villet 2005 [33]	Observational	Negative cumulative energy balance	Increased risk of ICU complications, especially infections
Alberda 2009 [74]	Observational	+ 1000 kCal/day + 30g Prot/day	Reduced mortality (Limited to BMI < 25 or ≥ 35)
Pichard 2008 [75]	Observational	Energy delivery greater than 1500 kCal over first 3 days	Reduced ICU and hospital mortality
Tsai 2010 [68]	Observational	< 60 % of energy target	Increased mortality
Weijs 2012 [76]	Observational	Meeting energy & protein targets	50% reduction in mortality
Abbreviations: BMI: Body mass index (kg/m2)			

There are problems with some of these studies. Specifically, Alberda et al [74] and Villet et al [33] did not adjust for illness severity and as such these observational data may simply point out the association between illness severity and difficulties with feeding. Furthermore, all of the above studies are observational and a causal relationship can therefore not be established. On the other hand, overfeeding is associated with a range of complications, including altered hepatic function, hyperglycemia, hypercapnia, increased infectious rates, increased inotropic support, increased body temperature, increased metabolic rate and measured energy expenditure.[28-30] Berger and Pichard [29] reported on a large multicentre Spanish study by Grau et al (2007) that found overfeeding at values as low as 110 – 120% of true requirements to be one of the determinants of altered hepatic function.

In conclusion, the provision of NT should be based on the Latin phrase “primum non nocere”, translated as “first, do no harm”.[30] Each patient should be closely monitored for signs and symptoms of overfeeding, as well as feeding intolerance and appropriate measures taken to avoid these complications. On the other hand, severe underfeeding can also be harmful and justifies continuous efforts to optimise nutrient delivery and feeding tolerance.[30]

2.5.4 Patient-specific recommendations

2.5.4.1 Obesity

Obesity (BMI > 30kg/m^2) may be present in up to 30% of ICU patients. The metabolic and endocrine consequences, such as glucose intolerance, insulin resistance, type 2 diabetes mellitus, metabolic syndrome, dyslipidemia, non-alcoholic fatty liver disease, and steatohepatosis, are further exacerbated by critical illness. Obese critically ill patients present with a greater increase in net glucose and protein oxidation and reduction in fat oxidation compared with their non-obese counterparts.[28,77-78] Problems with futile cycling, insulin resistance, and poor fuel utilization may predispose these patients to greater losses of lean body mass when in stressed situations and are therefore at greater risk of protein malnutrition.[28,78] They are also at increased risk of overfeeding due to the presence of comorbidities, such as diabetes, fatty liver and obesity-related hypoventilation syndrome. In fact many obese critically ill patients may present with worsened stress-induced hyperglycemia. In this setting, excessive calorie and glucose delivery may increase the risk of lipogenesis, hepatic steatosis, increased carbon dioxide production and increased work of breathing. Therefore special attention should be paid to the nutritional goals of obese patients in ICU.[28] Determination of the most appropriate energy target is difficult. However although conclusive evidence is lacking, expert opinion currently suggests restriction of energy intake to <70% of targeted energy intake [77] and high-protein feeding is recommended to preserve lean body mass, facilitate loss of fat mass and improve insulin sensitivity.[67,78] Table 2-10 indicates the nutritional guidelines for obese critically ill patients as published by the SCCM and ASPEN in 2009.[67]

Table 2-10 Nutritional guidelines (ASPEN) for obese critically ill patients [67]

	Recommendation
Energy	60 – 70 % of energy requirements 11 – 14 kcal/kg/day actual body weight 22 – 25 kcal/kg/day ideal body weight (Grade D recommendation)
Protein	≥ 2.0 g/kg ideal body weight/ day (Class I & II) (BMI 30 – 40) ≥ 2.5 g/kg ideal body weight/ day (Class III) (BMI ≥ 40)
Abbreviation: BMI: Body mass index	

Adequately powered RCTs are recommended to address the unresolved controversy regarding the amount of calories to be delivered to these patients, as well as the most accurate method to estimate energy requirements. Obesity-related changes in body composition and resting energy

expenditure, especially the reduced metabolic demands of adipose tissue and the variable increase in LBM with increasing body weight, makes the determination of both actual and ideal body weight (IBW) problematic. This puts the obese patient at risk of both under- and over-feeding. Using actual body weight has been shown to overestimate energy requirements, while IBW generally underestimates measured energy expenditure. Using an adjusted IBW takes into account the increase in metabolically active LBM mass that occurs with obesity. However, there is currently no consensus regarding which of these weights (actual, ideal, adjusted) should be used to predict energy requirements and some authors have proposed the use of a fixed amount of calories (e.g. 21kCal/kg actual body weight in obese ventilated patients).[28]

2.5.4.2 Malnutrition

There is also an increased incidence of malnutrition among ICU patients. Malnutrition is both a cause and consequence of disease and greatly impacts on clinical outcomes. NT in critical illness should therefore aim at preventing malnutrition [28] and providing more aggressive NT to those who are the most nutritionally at risk.[79] Accurate determination of the energy requirements of malnourished patients are however challenging. A certain subgroup of malnourished patients are also at risk of refeeding syndrome. High risk patients are those with a low body weight or BMI <18kg/m^2, a history of severe weight loss of ≥10% over 3 months, poor oral intake for >5 days and a history of poor nutritional intake or conditions that may be associated with malnutrition (e.g. alcoholism).[28]

2.5.4.3 Acute kidney injury (AKI)

AKI is a well-recognized hypermetabolic, pro-inflammatory and pro-oxidative state with distinct alterations in protein, carbohydrate and lipid metabolism.[80,81] This, together with coexisting catabolic illness leads to accelerated skeletal muscle breakdown with a negative nitrogen balance, insulin resistance, hyperglycemia, altered lipid metabolism, and water, electrolyte and acid-base imbalances.[81] Metabolic alterations and nutrient balances are further influenced by the modality and intensity of RRT (Grade B).[80] Currently the treatment modalities of choice in critically ill patients with AKI are continuous renal replacement therapies (CRRT), and especially continuous veno-venous hemofiltration (CVVH), veno-venous hemodiafiltration (CVVHD-F) or sustained low-efficiency dialysis (SLED). These therapies are known to exert a negative influence on electrolyte and nutrient balance due to their continuous or prolonged nature and high efficiency.[82]

Electrolyte and acid-base imbalances, such as hypo- and hypernatremia, hyperkalemia, hyperphosphatemia and metabolic acidosis are often seen in AKI.[80-82] These abnormalities can be resolved by appropriate regulation of the intensity of RRT and the composition of hemodialysis/hemofiltration fluids used.[80-82] Hypophosphatemia and hypomagnesemia caused by

the highly efficient modalities of RRT can be prevented by adequate electrolyte supplementation.[80,81,82] Potassium, magnesium and phosphate restrictions in PN are usually not needed if the patient is on daily RRT (CRRT, hemodialysis or SLED).[80] In enterally fed patients, the electrolyte content of most 1500–2000 kcal enteral formulae is usually adequate. However, electrolyte requirements can differ and requires individual assessment. Plasma electrolyte monitoring should aim at avoiding hypokalaemia and/or hypophosphataemia after the initiation of EN to prevent the so-called refeeding syndrome.[83]

Energy and macronutrient requirements in AKI are determined rather by the severity of the underlying disease, type and intensity of extracorporeal RRT, pre-existing nutritional status and acute/chronic comorbidities, than by the AKI per se.[81-83] A patient's tolerance of excessive substrate delivery (e.g. amino acids, trace elements, vitamins, etc) is severely reduced due to impaired renal regulatory function (C) [80] and overfeeding should therefore be avoided.[81] Saxena [81] suggests that a target of 25 – 30 kCal/kg during the first week of ICU care is appropriate for most stable patients. The energy target can then be increased to 35 kCal/kg/d if the patient is stable, in a low inflammatory state and weight gain is required.[81] According to Cano [80] energy targets should be adapted to the level of catabolism and tailored to individual needs in patients that are underweight or obese.

The optimal amount of protein intake in AKI patients is unknown. The use of high-flux filters and/or highly efficient modalities (such as CRRT or SLED) is associated with increased protein losses.[80,82] In CVVH/CVVHD-F there is a loss of ~0.2 g amino acids/L of ultrafiltrate (up to 10–15 g/day of amino acids), and 5 - 10 g/day of protein, depending on RRT modality and filter type. Approximately 10 – 15% of infused amino acids are lost in the dialysate/ultrafiltrate.[80] AKI patients on RRT should therefore receive at least 1.5g/kg/day of protein and an additional 0.2g/kg/day to compensate for protein and amino acid losses during RRT.[80,82] In non-catabolic AKI patients with milder non-oligouric forms of the syndrome that do not need RRT and who are likely to regain renal function in a few days lower protein intakes (up to 0.8 g/kg/d) will suffice for short periods of time, combined with adequate calorie intake (30 kcal/kg/d).[82] Table 2-11 indicates the nutritional requirements of patients with AKI as recommended by several authors.

Table 2-11 Nutritional requirements of patients with AKI

	NPE **kCal/kg/d**	**PROTEIN** **g/kg/d**	**CHO** **g/kg/d**	**LIPID** **g/kg/d**
Cano 2006 & 2009 (PN & EN) [80,83]	20 – 30	**Conservative therapy/ mild catabolism:** 0.6 – 0.8 (Max 1.0) **Extracorporeal therapy/ moderate catabolism:** 1.0 – 1.5 **CRRT/severe catabolism:** Up to max of 1.7	3 – 5 (Max 7)	0.8 – 1.2 (Max 1.5)
Fiaccadori 2010 [82]	20 – 25 (Max 30) BEE X 1.3	*Nitrogen:* Min of 0.25 *Protein:* 1.5 – 2.0 g/kg/d	-	~ 30 – 35% of NPE 0.8 – 1.2 over 18 – 24hr (Stop lipid infusion if s-TG >400mg/dL)
Martindale 2009 [67]	-	**RRT:** Increase up to a max of 2.5	-	-
Ziegler 2009 [84]	-	**No RRT:** 0.6 – 1.0 (based on renal function) **RRT:** 1.2 – 1.5	-	-
KDOQI [85] (NKF 2012)	25 – 35	**Non-catabolic/ no dialysis:** 0.8 – 1.0 **AKI on RRT:** 1.0– 1.5 **CRRT/hypercatabolic:** Up to a max of 1.7	-	-
Saxena 2012 [81]	25	**CT/mild catabolism:** 0.8 **Extracorporeal therapy/ moderate catabolism:** 1 – 1.5 **CRRT/SLED/severe catabolism:** 1.5–2.0	5	0.8 – 1.2

Abbreviations: AKI: Acute kidney injury; NPE: Non protein energy; CHO: Carbohydrates; PN: Parenteral nutrition; EN: Enteral nutrition; CRRT: Continuous renal replacement therapy; BEE: Basal energy expenditure according to Harris Benedict equation; s-TG: serum triglycerides; RRT: Renal replacement therapy; SLED: Sustained low efficiency dialysis

2.6 Impact of intravenous fluid therapy (IVFT) on actual nutrient intake

Most previous studies assessing energy intake among critically ill patients did not account for energy delivery from non-specific sources, such as dextrose water and propofol. Table 2-12 shows a summary of the NNES that were taken into account by observational studies that were published prior to the data collection phase of our study. This table is based on the energy sources that were reported by the respective authors.

Table 2-12 NNES taken into account by previously published observational studies

	IV fluid therapy			**Drug dilution**	**50% dextrose water**	**Propofol**	**Polygam**
	Crystalloids	**HES**	**Albumin**				
Villet 2005 [33]	X			X		X	
Hise 2007 [34]	X					X	
Alberda 2009 [74]						X	
Tsai 2011 [68]	X						
Arabi et al 2011 [70]	X					X	
This study	X	X	X	X	X	X	X

The prospective cohort study by Hise et al [34] found that medical ICU patients received less propofol and significantly less dextrose-containing IV fluids when compared to surgical ICU patients. On average, patients in the surgical ICU received 250 kcal per day from propofol and dextrose-containing fluids. These NNES contributed a clinically relevant amount of kilocalories in surgical ICU patients.[34] Both Hise et al [34] and Taylor et al [86] found propofol to be a significant source of lipids in ICU patients and they recommend that close monitoring of propofol administration when calculating feeding prescriptions is essential to prevent excessive lipid intake.[34,86] According to Hise et al [34] the significantly higher energy intake derived from dextrose-containing IV fluids in their surgical ICU was attributed to the greater need for fluid resuscitation in perioperative patients, as well as differences among ICU physician practices regarding volume and duration of dextrose-containing IV fluid administration. They recommended routine monitoring of all NNES. In a RCT by Arabi et al [70] the average daily caloric intake derived from propofol and dextrose infusions was 34kCal/day and 116kCal/d respectively. The authors did not specify the sources of dextrose energy that were evaluated.

According to Byrnes et al [31] additional energy delivery from NNES is of great concern in patients at risk of refeeding syndrome. According to a recent review article by Berger and Pichard [29] the concept of counting only NPE, as well as not taking into account the energy derived from NNES, such as glucose 5% solutions and fat soluble sedatives, might have been responsible for systematic overfeeding in several studies. The authors strongly suggest taking into account the energy content of inadvertent NNES when prescribing energy targets.

2.7 Conclusion

Optimal fluid and electrolyte administration forms a cornerstone in the successful management of critical illness-induced fluid and electrolyte imbalances. Nevertheless, ICU physicians face difficulty in optimising patients' fluid status on a daily basis.[20] Nutrient, water, mineral and electrolyte balance are all closely related [21] and achieving and maintaining balance plays a crucial role in obtaining the full benefit from NT.[22] NT also directly impacts on a patient's fluid and electrolyte status, since the delivery of NT cannot be separated from that of fluid and electrolytes.[21,25] Excess fluid intake from multi-drug infusions, PN or EN or antibiotics requiring large volume infusions, should be subtracted from the maintenance fluid regimen in order to avoid fluid overload.[39] Similarly IVFT in patients receiving CRRT for AKI should also compensate for increased fluid given to provide adequate nutrition and drugs, however most ICUs do not take into account fluid delivery in their prescription of fluid removal.[10]

Calculation of fluid and electrolyte requirements is as important as determining a patient's macro- and micronutrient needs when prescribing NT [21,25] and daily monitoring of fluid and electrolyte status should be incorporated into the dietician's daily ICU round. Input and output charts provide valuable information on fluid status,[25] however, frequent errors in the measurements and records often result in a large cumulative error in fluid balance. There are currently few studies that have recorded accurately total fluid and electrolyte delivery.

In addition most studies that have assessed energy intake among critically ill patients did not take into account additional energy delivery from inadvertent NNES. The small number that did, did not include all the NNES that form part of daily routine ICU practices. As such it is not known to what extent the latter would have further contributed to total energy intake. An accurate determination of the contribution of NNES to total energy delivery is paramount, since both over- and underfeeding are associated with detrimental effects.

CHAPTER 3

METHODOLOGY

3.1 Aim

To determine the nutritional content / contribution of IV fluid and electrolyte administration on the total feeding prescription of ICU patients admitted to a multidisciplinary ICU.

3.2 Specific objectives

- To determine the volume and types of IV fluids most often prescribed to ICU patients
- To determine the IV electrolyte supplements (type and dosing) most often prescribed to ICU patients
- To determine the contribution of the following routine ICU practices on a patient's total fluid, electrolyte, energy and macronutrient intake:
  - Crystalloids, colloids and blood products used for IVFT
  - Crystalloids used for IV drug dilution and flushing of IV lines
  - IV electrolyte replacement
  - Lipids delivered with sedatives (propofol)
  - Dextrose water used in the treatment of hypoglycaemia and hyperkalaemia
  - Sucrose delivered with immunoglobulin therapy (polygam)
- To compare a patient's total energy and protein intake inclusive of nutritional and non-nutritional sources with his/her estimated energy and protein targets.

3.3 Implementation objectives

The results from this study will aid clinical dieticians to optimise the nutritional care of critically ill patients by taking into account the contribution of IV fluid and electrolyte administration to a patient's total fluid, electrolyte, energy and macronutrient intake. It will also function as an audit of actual delivery.

3.4 Study design

A retrospective descriptive observational study was conducted.

3.5 Study population and sampling

3.5.1 Study population

The study population consisted of critically ill adult (i.e. ≥ 18 years of age) patients admitted to the general intensive care unit (GICU) of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

3.5.2 Sampling method

All patients discharged from ICU or who demised on or after the first day of data collection, were screened for eligibility. Consecutive patients meeting the inclusion criteria were enrolled in the study until the required sample size was reached. Data collection commenced on the 19th of March 2012 and was completed on the 17th of July 2012.

3.5.3 Inclusion and exclusion criteria

3.5.3.1 Inclusion criteria

- Adults (≥ 18 years of age)
- Must have been admitted to the GICU of CMJAH
- APACHE II score ≥10 on admission to ICU
- Must have received NT (i.e. EN and/or PN) for at least 72 hours.
- Must have had an ICU length of stay of at least 72 hours.

3.5.3.2 Exclusion criteria

- Skeletal abnormalities, contractures and spinal cord injuries (quadriplegia and paraplegia)
- NT discontinued within 72 hours after ICU admission.
- Patients that were discharged from ICU or that demised within 72 hours after ICU admission.

3.5.4 Sample size

A total of seventy one patients (n=71) were included in the final sample size. This was based on a precision of Cp= 12% and a confidence interval of 95% (Appendix A).

3.6 Methods of data collection

Data collection was carried out in the 12-bed GICU of CMJAH. All patients discharged from ICU or who demised on or after the first day of data collection were screened for eligibility, i.e. all data were collected retrospectively. ICU charts and hospital files of eligible patients' were reviewed to collect data from ICU admission until ICU discharge, or until discontinuation of NT or death, whichever occurred first. All relevant data were entered into standardised case report forms following a standardised data collection protocol (Appendix B). If a study participant remained in ICU for more than 7 days data were collected until day 7 in ICU.

3.6.1 Baseline patient data

Study participants' ICU charts and hospital files were reviewed retrospectively in order to obtain the following baseline information:

- Age, sex, ICU admission date/time, type of admission (medical versus surgical) and primary ICU diagnosis.
- As an indicator of the severity of disease on admission to ICU, data from the first 24 hours after ICU admission was used to calculate the patient's Acute Physiology and Chronic Health Evaluation (APACHE II) score. For each APACHE variable, the single worst value out of all values from the first 24 hours after ICU admission was used. If variables were not available from the first 24 hours, data outside the 24 hour window but closest to ICU admission were used.
- Additional medical information was charted if applicable to the study participant's feeding prescription (e.g. comorbidities or nutrition-related problems, medical history, arterial blood gas values, biochemistry, fluid balance, gastric residual volumes, prescribed medication/s, tests/procedures, clinical presentation and feeding tolerance).
- Renal function and the presence of severe sepsis or septic shock were reviewed over the entire study period; i.e. from ICU admission until study exit. The presence of severe sepsis/SIRS or septic shock was based on the charted diagnoses and/or reviewing study participants' ICU charts for the presence of sepsis criteria [87] as specified in the standardised data collection protocol (Appendix B). The presence of AKI was based on the charted diagnoses by the attending physician.

3.6.2 Baseline anthropometrical data

3.6.2.1 Height

Height charted on the study participant's ICU chart was used. Height is routinely estimated and charted by the registered dietician for all ICU patients according to the "recumbent height" method.[17]

3.6.2.2 Body weight (BW)

Weight charted on the study participant's ICU chart was used. Estimated dry weight is routinely charted by the registered dietician for all patients in the ICU. Weight charted for patients with fluid retention or amputation/s are routinely estimated according to standardized methods (Appendix C).[17]

3.6.3 Daily feeding prescription/s

The daily feeding prescription/s as charted by the registered dietician (RD) or the study participant's attending physician were recorded retrospectively for each study participant.

3.6.4 Daily fluid and nutritional data

3.6.4.1 Type of nutrition delivered

The type and route of nutrition delivered to a study participant (EN and/or PN and/or oral nutrition) was recorded.

3.6.4.2 Fluid, electrolyte, energy and macronutrient intake

- The type and volume of IV fluids used for IVFT
- The volume of liquid drugs administered via the IV, enteral or oral route
- The type and volume of IV fluids used for reconstitution and dilution of IV drugs
- The type and volume of IV fluids used for flushing of IV lines
- The type and dosing of IV electrolyte replacement (if prescribed)
- The dose of propofol, dipeptiven and/or polygam infused (if prescribed)
- The type and volume of dextrose water administered as part of standard ICU protocols
- The type and volume of EN and/or PN
- The type and volume of fluids and/or feeds taken orally (if applicable)

3.7 Pilot study

A pilot study was undertaken in the GICU of CMJAH to determine the completeness and accuracy of the following:

- Patients' ICU charts for data collection purposes
- Data entry procedure (case report forms)
- Data coding procedure

Ten patients (n=10) were included in the pilot study and they were subsequently excluded from the main study.

3.8 Data management and analysis

3.8.1 Statistical analysis

MS Excel was used to capture the data and STATISTICA version 9 (StatSoft Inc. (2009) STATISTICA (data analysis software system), www.statsoft.com.) was used to analyse the data.

Summary statistics were used to describe the variables. Distributions of variables are presented with histograms and/or frequency tables. 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.

Relationships between two continuous variables were analysed with regression analysis and the strength of the relationship measured with Pearson correlation, or Spearman correlation if the continuous variables were not normally distributed. The relationships between continuous response variables and nominal input variables (like different diets) were analysed using appropriate analysis of variance (ANOVA).When ordinal response variables were compared versus a nominal input variable, non-parametric ANOVA methods were used. For completely randomized designs the Mann-Whitney test or the Kruskal-Wallis test were used. The relation between nominal variables were investigated with contingency tables and appropriate chi-square tests like the likelihood ratio chi-square test.

A p-value of $p < 0.05$ represented statistical significance in hypothesis testing and 95% confidence intervals were used to describe the estimation of unknown parameters.

3.8.2 Analysis of anthropometrical data

3.8.2.1 Ideal body weight

Ideal body weight was calculated as follows (Table 3-1):

Table 3-1 Ideal body weight calculations: [88]

Males: Height^2 (m) X 20 – 25
Females: Height^2 (m) X 19 - 24
(Height obtained from ICU charts)

3.8.2.2 Nutritional status

Nutritional status was determined by using the body mass index (BMI) classification system (Table 3-2):

Table 3-2 Nutritional status according to BMI classification system [17]

Nutritional status		**BMI classification***
Undernourished	Grade I	17 ≤ BMI < 18.5
	Grade II	16 ≤ BMI < 17
	Grade III	BMI < 16
Normal		18.5 ≤ BMI < 25
Overweight		25 ≤ BMI < 30
Obese	Class I	30 ≤ BMI < 35
	Class II	35 ≤ BMI < 40
	Class III (Morbid obesity)	BMI ≥ 40
* BMI (kg/m2) = weight/ (height)^2 (Weight and height obtained from ICU charts)		

3.8.3 Analysis of fluid and nutritional data

Daily fluid and nutritional data were used to determine the following:

- **Total fluid delivery**

Total fluid delivery included fluid administered via the IV route (i.e. IVFT, IV drug administration, reconstitution and dilution of IV drugs, IV electrolyte and vitamin supplementation, flushing of IV lines, dextrose water administered in the treatment of hypoglycemia and hyperkalemia, PN), enteral route (i.e. EN, water, flushing of feeding tube, drugs administered via the enteric tube, including the mixing of crushed medication with water) and oral route if applicable.

- **Total electrolyte delivery**

Total electrolyte delivery included electrolytes administered via the intravenous route (i.e. electrolyte-containing IV solutions used for IVFT, drug dilution and flushing of IV lines, IV electrolyte replacement, PN), enteral route (EN and/or fluids administered via feeding tube) and oral route if applicable.

- **Total energy delivery with delineation of energy sources**

Total energy delivery included energy delivery from NT (EN, PN and/or dipeptiven), additional oral intake (if applicable), NNES (crystalloids and colloids used for IVFT, drug dilution and flushing of IV lines), lipids delivered with sedatives (*propofo*l), sucrose delivered with immunoglobulin therapy (*polygam*) and IV dextrose administration in the treatment of hypoglycemia and hyperkalemia.

- **Macronutrient distribution**

The percentage (%) macronutrient distribution of mean daily energy intake was determined.

- **Estimated energy and protein balance**

Estimated energy/protein balance was calculated on a daily basis as total energy/protein delivery – total energy/protein target*. The cumulative energy/protein balance (total energy/protein delivery – total energy/protein target* for the total study period) was then calculated.[33-34]

- **Energy and protein delivery in relation to estimated targets**

For energy/protein analyses comparing delivery of nutrition in relation to estimated targets*, the outcome variable were mean energy/protein delivery in the ICU relative to estimated targets*. Each study participant's actual energy/protein intake in kilocalories/grams per day was divided by the

target value in kilocalories/grams per day. The mean percent target per ICU day was calculated as follows (Table 3-3):

Table 3-3 Calculation of mean percent target: [34]

Mean percent target (energy): = ∑ (Each day's energy intake/target energy intake) X 100 7 days
Mean percent target (protein): = ∑ (Each day's protein intake/target protein intake) X 100 7 days

***Estimated energy and protein targets:**

The charted daily feeding prescriptions did not always reflect the study participants' actual energy and protein targets for the following reasons:

- Feeding prescriptions written by the attending doctor in the absence of the RD was not based on calculated nutritional targets. The RD's ICU round takes place in the mornings and henceforth patients admitted in the afternoon or at night had feeding prescriptions written by the attending doctor until the next RD round.
- In some instances more than one feeding prescription was charted on a particular day.
- Certain specialised feeding prescriptions did not reflect the patient's actual energy and protein targets, e.g.
  - Trickle/trophic feeding
  - Low electrolyte feeding prescription in the presence of severe electrolyte derangements (e.g. hypernatremia > 160mmol/L)

Henceforth the study participants' daily energy and protein targets, expressed in ranges (e.g. 20 – 25kCal/kg and 1.2 – 1.5g/kg protein), were standardized retrospectively according to a standardized procedure, as indicated in the standardized data collection protocol (Appendix B). This procedure was based on the evidence-based recommendations made by the European Society of Enteral and Parenteral Nutrition (ESPEN), [65-66] American Society of Parenteral and Enteral Nutrition (ASPEN) [67] and the Canadian Clinical Practice Guidelines (CCPG).[64] The weight used for calculating nutritional targets were based on the standardized procedure as indicated in

the standardized data collection protocol (Appendix B).[88-90] Meeting 100% of energy/protein target was defined as an energy/protein delivery falling between 90% of the minimum and 110% of the maximum target. Underfeeding was defined as meeting less than 90% of the minimum energy/protein target and overfeeding as meeting more than 110% of the maximum energy/protein target.

3.9 Time schedule

Table 3-4 Time schedule

2011 – 2012	**Nov-11**	**Dec-11**	**Jan-12**	**Feb-12**	**Mar-12**	**Apr-12**	**May-12**	**Jun-12**	**Jul-12**	**Aug-12**	**Sep-12**	**Oct-12**	**Nov-12**	**Dec-12**
	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week
	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4
Finalise protocol & ethics approval														
Pilot study														
Data collection														
Preparing data for analysis														
Analysing data														
2013	**Jan-13**	**Feb-13**	**Mar-13**	**Apr-13**	**May-13**	**Jun-13**	**Jul-13**	**Aug-13**	**Sep-13**	**Oct-13**	**Nov-13**	**Dec-13**	**Jan-14**	**Feb-14**
	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week	Week
	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4
Analysing data														
Write thesis														
Submit final thesis														

3.10 Ethical and legal considerations

The study was approved by the University of Stellenbosch Health Research Ethics Committee 2 (S12/01/001) and the University of the Witwatersrand Human Research Ethics Committee (M120240).

Written permission has been granted by the following respective persons at CMJAH (letters of permission available on request):

- Director of Critical Care and Head of GICU where study was conducted (Prof GA Richards)
- Chief Executive Officer of CMJAH (Dr TE Selebano)

Study participants' identities (names and hospital numbers) were known to the data collector since they are routinely charted. However, identifiable data were coded and "links" kept separate. All patients discharged from ICU or who demised on or after the first day of data collection were entered into a screening log (Appendix B). Each patient's name and hospital number were recorded on the screening log. Screening log columns represented eligibility criteria for purposes of data collection. A research number was allocated to all eligible patients and recorded on the screening log. Research numbers were allocated consecutively from R1 to R71 as patients were entered into the study. Each eligible patient's data were then recorded on an individual data entry form coded with only his or her unique research number. The screening log is kept safe and only the investigators have access to it. The screening log will help track down which patient corresponds to which research number in case there are data queries at a later date. All data were handled with strict confidentiality and none other than the investigators had access to the data. Data was made anonymous for analysis.

CHAPTER 4

RESULTS

4.1 Baseline characteristics

Seventy-seven patients were enrolled out of three-hundred and nine consecutive admissions (24.9%): six patients were excluded due to incomplete data or missing charts, leaving seventy-one patients for analysis. Figure 4-1 shows a detailed flow chart for the inclusion of study participants.

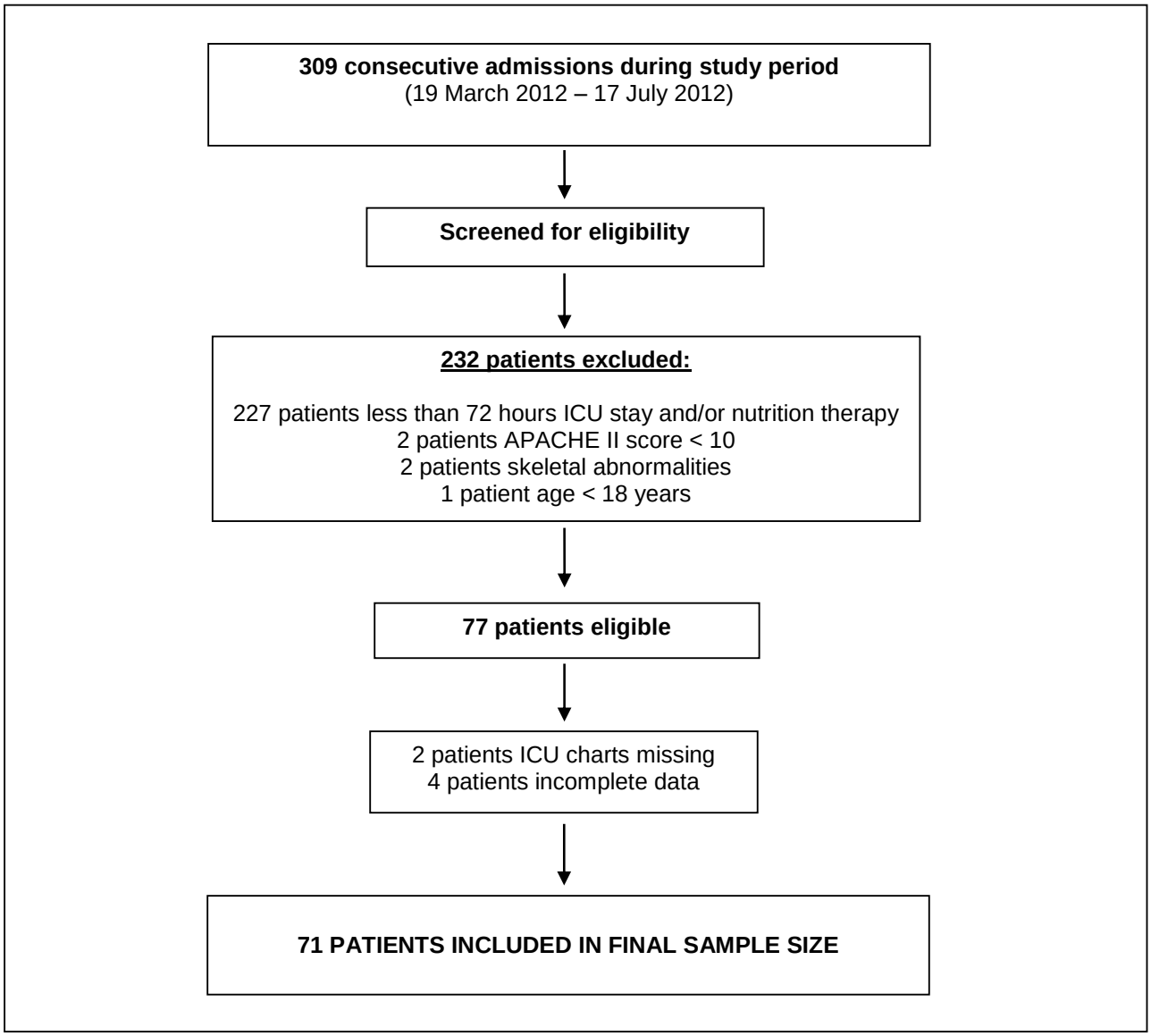

Figure 4-1 Flow chart for inclusion of study participants

The final sample size (n=71, mean age 49.2 ± 17.1 years) had an equal gender distribution with 49% being male and 51% female. Of the seventy-one study participants, 68% were medical and 32% surgical admissions. Study participants were mostly admitted for severe sepsis (28.2%), respiratory (23.9%), neurological (18.3%) and gastrointestinal conditions (14.1%). On admission to ICU study participants had an average APACHE II score of 21.0 ± 6.1 and an average body mass index (BMI) of 28.5 ± 8.1 kg/m^2. Study participants' fluid and nutrient intake were reviewed over a mean of 5.7 ± 1.1 days (median 6.3, range 3.5 – 7.0); i.e. the time elapsing from ICU admission until study exit. Study participants' baseline characteristics are reported in Table 4-1.

Table 4-1 Baseline characteristics of study participants (n=71)

Variables	Unit	Mean ± SD (median)	Range
Sex	(N, %)		
Male		35 (49)	
Female		36 (51)	
Age	Years	49.2 ± 17.1 (47.4)	18.0 – 85.0
APACHE II, admission		21.0 ± 6.1 (22.0)	10.0 – 34.0
Admission category	(N, %)		
Medical		48 (68)	
Surgical		23 (32)	
Primary admission diagnosis	(N, %)		
Gastrointestinal		10 (14.1)	
Sepsis		20 (28.2)	
Neurological		13 (18.3)	
Respiratory		17 (23.9)	
Other		11 (15.5)	
Body height	cm	167.3 ± 8.6 (166.0)	150.0 – 186.0
Body weight	kg	79.1 ± 20.6 (75.0)	45.0 – 150.0
BMI	kg/m^2	28.5 ± 8.1 (26.8)	16.7 – 55.1
Ideal body weight	kg	61.6 ± 7.3 (61.0)	48.4 – 78.0

Data are presented as N (%), mean ± SD (median) and ranges.

Abbreviations: APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: Body mass index

4.2 Presence of severe sepsis, septic shock and AKI

The presence of severe sepsis, septic shock and AKI throughout the study period is reported in table 4-2. Fifty-eight study participants (81.7%) presented with severe sepsis/SIRS or septic shock during the period of observation. A total of thirty-one study participants (43.6%) presented with AKI. Sixteen participants (22.5%) received dialysis in the form of SLED or CVVHD (Table 4-2). A significant association was found between severity of illness (APACHE II score) on admission to ICU and the presence of AKI, as well as the probability of receiving subsequent dialysis (p=0.00009) (Table 4-2).

Table 4-2 Severe sepsis, septic shock and AKI during study period

Variables	N	%	APACHE II score (mean ± SD)
Presence of severe sepsis/shock	58	81.7	-
Presence of acute kidney injury			
AKI- no dialysis	15	21.1	22.3 ± 5.7
AKI- dialysis	16	22.5	25.8 ± 4.7
Normal renal function	40	56.3	18.6 ± 5.5

Data are presented as N (%), mean ± SD (median).

Abbreviations: AKI: Acute kidney injury; APACHE II: Acute Physiology and Chronic Health Evaluation II

The incidence of AKI was similar among medical and surgical participants. Ten (44%) of the twenty-three surgical participants and twenty-one (44%) of the forty-eight medical participants presented with AKI (including dialysed and non-dialysed participants). A greater percentage of medical participants received dialysis compared to surgical participants (29% versus 19% respectively, p= 0.045, chi-square test).

4.3 Fluid delivery

Table 4-3 shows a breakdown of the following:

(1) Total cumulative fluid delivery over the entire study period

(2) Mean daily fluid delivery

(3) Breakdown of fluid delivery according to route of delivery (IV, enteral and oral)

Table 4-3 Breakdown of total cumulative fluid delivery

Variables	N-size	Cumulative delivery (litres)		% of total cumulative fluid delivery	
		Mean ± SD (median)	Range	Mean ± SD (median)	Range
TOTAL CUMULATIVE DELIVERY [A]	71	18.3 ± 4.8 (18.0)	7.0 – 31.1	-	-
Mean daily delivery (L/d)	71	3.2 ± 0.6 (3.2)	1.7 – 5.2	-	-
Mean daily delivery (mL/kg/d)	71	50.0 ± 11.6 (48.0)	29.0 – 86.4	-	-
BREAKDOWN ACCORDING TO ROUTE OF DELIVERY					
INTRAVENOUS	71	11.8 ± 5.6 (10.5)	2.1 – 30.9	62.5 ± 18.2 (58.0)	30.4 - 100
Fluid therapy	71	6.0 ± 3.2 (5.2)	0.3 – 15.0	32.0 ± 12.0 (31.4)	4.3 – 55.4
Crystalloid	70	4.5 ± 2.5 (3.8)	0.6 – 10.7	24.0 ± 10.7 (23.9)	4.6 – 49.5
Colloid	56	1.2 ± 0.9 (1.0)	0.3 – 3.3	6.2 ± 3.9 (5.7)	1.0 – 17.5
Blood products	41	1.2 ± 1.6 (0.6)	0.3 – 8.0	6.0 ± 6.1 (3.7)	1.3 – 25.8
Drug administration [B]	71	3.9 ± 2.0 (3.9)	0.7 – 11.2	20.7 ± 8.1 (21.4)	4.2 – 49.2
Flushing of lines	71	0.5 ± 0.1 (0.5)	0.2 – 1.0	2.9 ± 0.9 (2.7)	1.7 – 7.0
Electrolyte & vitamin supplementation	70	0.1 ± 0.1 (0.1)	0 – 0.7	0.7 ± 0.5 (0.6)	0.0 – 2.5
Nutrition	16	4.8 ± 2.8 (4.0)	0.8 – 10.0	23.9 ± 15.5 (23.1)	3.2 – 51.3
Propofol	7	0.8 ± 0.7 (0.6)	0.1 – 2.2	5.2 ± 4.5 (3.3)	1.4 – 13.6
Other [C]	41	0.1 ± 0.1 (0.1)	0 – 0.4	0.6 ± 0.4 (0.4)	0.1 – 1.7
ENTERAL	70	6.5 ± 3.1 (6.4)	0.1 – 12.9	37.8 ± 17.8 (41.2)	0.7 – 69.6
Nutrition	67	6.3 ± 2.7 (5.9)	0.4 – 10.8	36.9 ± 16.0 (38.6)	1.9 – 68.5
Flushing of enteric tube	63	0.1 ± 0.1 (0.1)	0.0 – 0.3	-	-
Tap water for hypernatremia	5	1.0 ± 0.8 (0.9)	0.1 – 1.8	-	-
Other enteral fluids	69	0.3 ± 0.2 (0.2)	0 – 1.3	-	-
ORAL [D]	15	0.3 ± 0.6 (0.2)	0.0 – 2.3	1.5 ± 2.2 (1.1)	0.2 – 9.0

Data are presented as mean ± SD (median) and ranges.

[A]Total cumulative delivery: Total cumulative fluid delivery (litres) over total study hours.

[B]Drug administration: Volume of drugs in liquid form, as well as fluids used for reconstitution and dilution purposes

[C]Other: Administration of 50% dextrose water in the treatment of hyperkalemia and hypoglycaemia

[D]Oral: Nutrition (e.g. sipfeeds), water and liquid drugs (e.g. Ulsanic, Mist KCl)

4.3.1 Routes of fluid delivery

Figure 4-2 shows the contribution of IV, enteral and oral fluid administration to total cumulative fluid delivery. IV fluid administration (n=71) contributed 62.5 ± 18.2% (median 58.0, range 30.4 - 100) to total fluid delivery (TFD). Enteral fluid administration (n=70) contributed 37.8 ± 17.8% (median 41.2, range 0.7 – 69.6) to TFD whereas oral fluids (n = 15) only contributed 1.5 ± 2.2% (median 1.1, range 0.2 – 9.0).

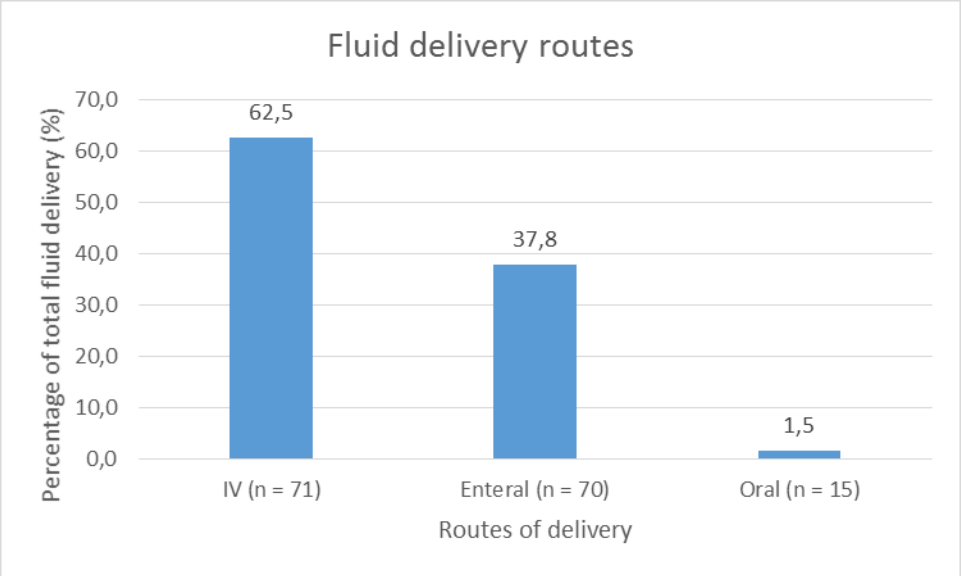

Figure 4-2 Breakdown of total cumulative fluid delivery according to route of administration

4.3.2 IV fluid delivery

IV maintenance or resuscitation crystalloids, colloids and blood products contributed 52.0 ± 16.0% (median 54.7, range 10.6 – 82.1) to total cumulative IV fluid delivery. IV drug administration contributed a further 35.2 ± 13.5% (median 32.1, range 10.7 – 68.7). This included the volume of liquid drugs, as well as fluids used for reconstitution and dilution purposes. PN and IV line flushing contributed 5.8 ± 13.1% (median 0 – 53.7) and 5.2 ± 3.1% (median 4.4, range 1.9 – 23.1) respectively. The remaining IV fluid volume was derived from electrolyte/vitamin supplementation and 50% dextrose water with a mean contribution of 1.1 ± 1.1% (median 0.8, range 0 – 7.2) and 0.6 ± 0.9% (median 0.3, range 0 – 5.64) respectively. Fifty percent (50%) dextrose water was administered as part of the unit's protocol for the management of hypoglycemia and/or hyperkalemia. Figure 4-3 shows a breakdown of total cumulative IV fluid delivery across all study participants who received IV fluids (n=71).

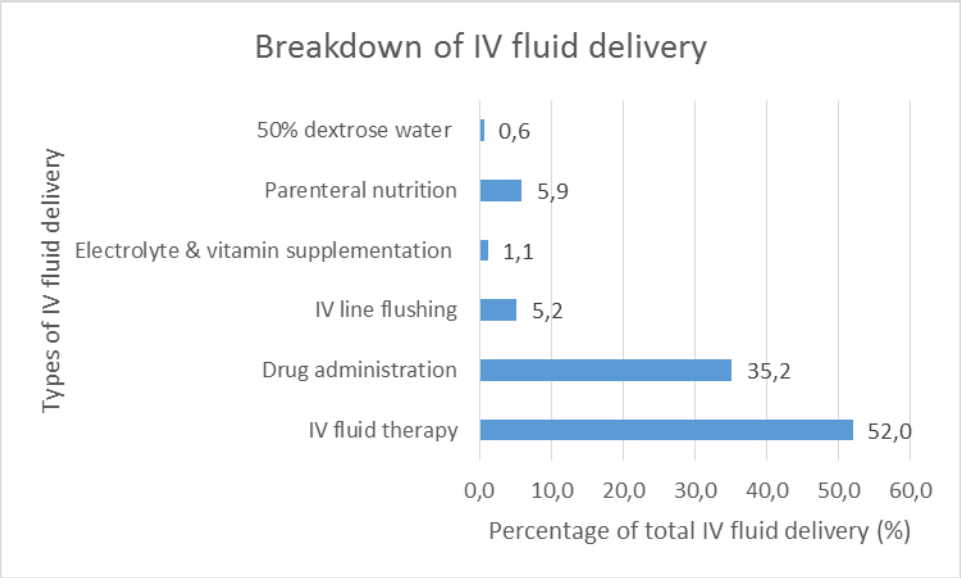

Figure 4-3 Mean percentage breakdown of cumulative IV fluid delivery (n=71)

4.3.2.1 IV fluid therapy (IVFT)

Figure 4-4 shows a breakdown of total cumulative IVFT across all study participants who received IVFT (n=71).

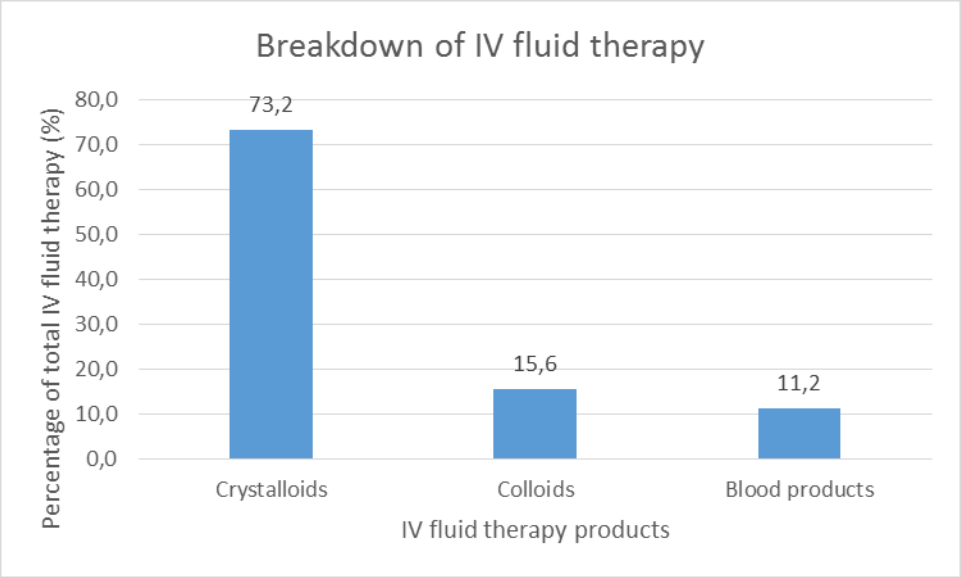

Figure 4-4 Mean percentage breakdown of total cumulative IV fluid therapy (n=71)

More than two-thirds of the cumulative IVFT volume was derived from crystalloids with a mean contribution of 73.2 ± 20.3% (median 76.6, range 0 – 100). Colloids contributed 15.6 ± 12.3% (median 16.1, range 47.5) and blood products 11.2 ± 18.1% (median 4.7, range 0 – 100). Table 4-4 shows the mean daily volume of the different IV fluids administered as part of IVFT.

Table 4-4 Mean daily volume of different IV fluids used for IV fluid therapy (IVFT)

Variables	Unit	N-size[A]	Mean ± SD (median)	Range
Mean daily IVFT volume	L/d	71	1.1 ± 0.5 (1.0)	0.1 – 2.5
Crystalloids	L/d	70	0.8 ± 0.4 (0.7)	0.1 – 1.9
Glucose solutions[B]	L/d	39	0.4 ± 0.3 (0.3)	0.02 – 1.2
Sodium chloride solutions[C]	L/d	13	0.3 ± 0.3 (0.2)	0.005 – 1.2
Gluco-saline solutions[D]	L/d	13	0.3 ± 0.3 (0.3)	0.009 – 1.2
Electrolyte solutions[E]	L/d	65	0.5 ± 0.4 (0.4)	0.01 – 1.5
Colloids	L/d	56	0.2 ± 0.1 (0.2)	0.04 – 0.6
Blood products	L/d	41	0.2 ± 0.3 (0.1)	0.04 – 1.3
Platelets	L/d	4	0.2 ± 0.1 (0.2)	0.1 – 0.3
Erythrocyte concentrate	L/d	40	0.1 ± 0.1 (0.1)	0.04 – 0.7
Fresh frozen plasma	L/d	11	0.2 ± 0.1 (0.2)	0.04 – 0.4

Data are presented as mean ± SD (median) and ranges.

[A] N-size: Number of study participants who received the given IV fluid

[B] Glucose solutions: 5% dextrose water & anticoagulant citrate dextrose solution

[C] Sodium chloride solutions: Normal and hypertonic saline

[D] Gluco-saline solutions: Rehydration solution (Dextrose 5% in 0.45% saline)

[E] Electrolyte solutions: Balsol/Plasmalyte B and Ringer's lactate/Hartman's solution

Crystalloids

Crystalloid solutions were administered to seventy (98.6%) of the seventy-one study participants (n=70) with a mean daily volume of 0.8 ± 0.4 litres (Table 4-4). Electrolyte solutions (balanced) were most often prescribed with a mean contribution of 61.2 ± 34.8 % (median 61.6, range 0 – 100) to total cumulative crystalloid delivery. The percentage contribution of glucose-, gluco-saline- and sodium chloride solutions were 26.0 ± 30.4% (median 12.4, range 0 – 100), 7.9 ± 21.9% (median 0, range 0 – 100) and 4.9 ± 15.0% (median 0, range 0 – 100) respectively. Figure 4-5 shows the mean percentage breakdown of total cumulative crystalloid delivery (n=70).

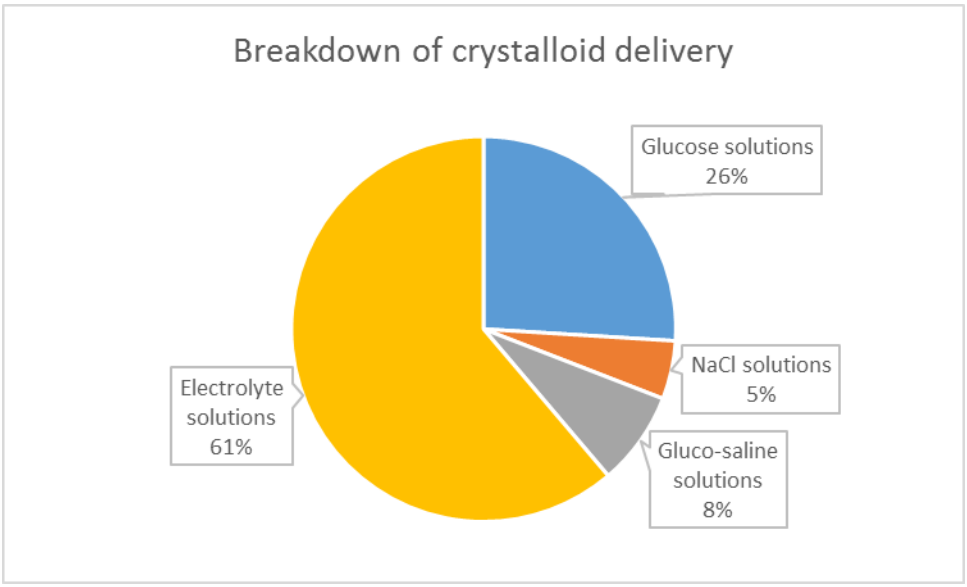

Figure 4-5 Mean percentage breakdown of total cumulative crystalloid delivery (n=70)

Colloids

Colloid solutions were administered to fifty-six (78.9%) of the seventy-one study participants (n=56) with a mean daily volume of 0.2 ± 0.1 litres (Table 4-4). The primary colloid used was non-hypertonic LMW 130/0.4 KD hydroxyethyl starch (HES) with a mean contribution of 99.4 ± 3.1 % (median 100, range 81.3 – 100) to total colloid delivery. IV albumin and gelatin solutions (n=2) contributed a negligible 0.6 ± 3.1 % (median 0, range 0 – 18.7) and were therefore not considered for statistical analyses (Figure 4-6).

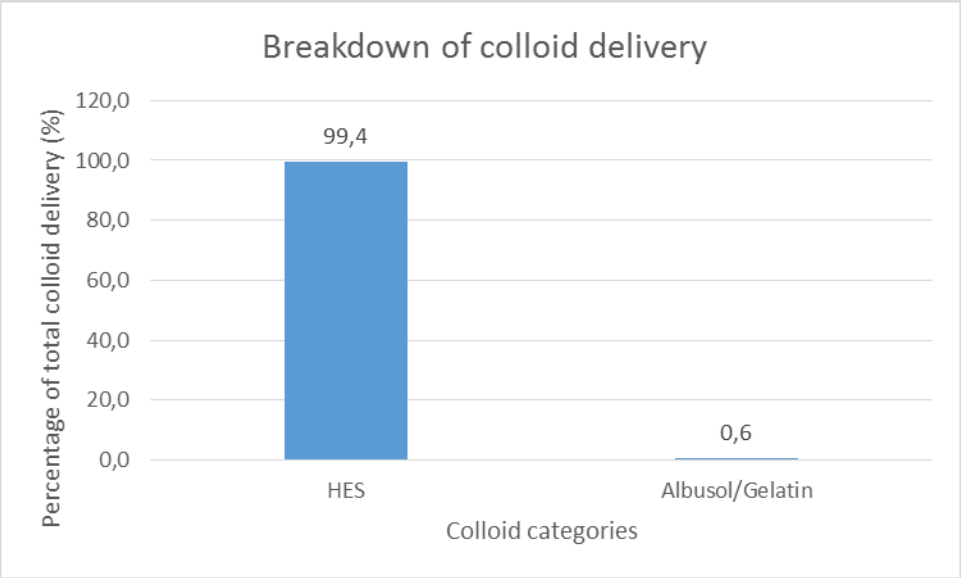

Figure 4-6 Mean percentage breakdown of total cumulative colloid delivery (n=56)

Blood products

Blood products were administered to forty-one (57.7%) of the seventy-one study participants (n=41) with a mean daily volume of 0.2 ± 0.3 litres (Table 4-4). Figure 4-7 shows a breakdown of the blood products used for IVFT (n=41).

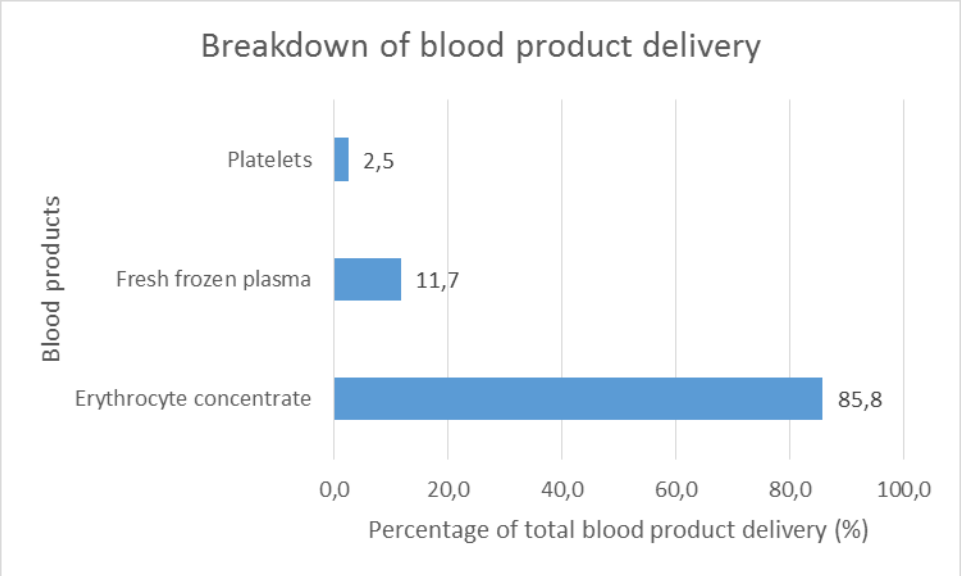

Figure 4-7 Mean percentage breakdown of total cumulative blood product delivery (n=41)

Erythrocyte concentrate was most often prescribed with a mean contribution of 85.7 ± 25.7 % (median 100, range 0 – 100) to total cumulative blood product delivery. Fresh frozen plasma and

platelets contributed a further 11.7 ± 22.5 % (median 0, range 0 – 100) and 2.5 ± 9.1 % (median 0, range 0 – 51.1) respectively.

4.3.3 Fluid delivery according to admission category and renal function

Surgical participants received a significantly higher mean daily fluid delivery (L/day: p<0.01; mL/kg/d: p=0.002) compared to their medical counterparts and was due to significantly more IVFT administered to the former group (p=0.00002). Daily crystalloid, colloid and blood product delivery were significantly higher among surgical participants (p=0.02, p=0.01, p=0.01, respectively) with a significantly higher percentage contribution of IVFT to TFD in this patient subgroup (39.5 vs 28.4%, p=0.001) (Table 4-5).

Table 4-5 Total fluid delivery and intravenous fluid therapy according to admission category

	Unit	Surgical	N	Medical	N	p-value
TFD						
Total cumulative	L	19.6 ± 5.0	23	17.6 ± 4.6	48	0.099
Mean daily	L/d	3.6 ± 0.6	23	3.0 ± 0.6	48	<0.01
Mean daily	mL/kg/d	56.1 ± 12.0	23	47.1 ± 10.3	48	0.002
Mean daily IVFT	L/d	1.4 ± 0.6	23	0.9 ± 0.4	48	0.00002
Crystalloids	L/d	0.9 ± 0.4	23	0.7 ± 0.4	47	0.02
Colloids	L/d	0.30 ± 0.2	19	0.16 ± 0.1	37	0.01
Blood products	L/d	0.29 ± 0.33	19	0.14 ± 0.15	22	0.01
Contribution to TFD (%)						
IVFT	%	39.5 ± 11.8	23	28.4 ± 10.4	48	0.0001

Data are presented as mean ± SD. Statistical analyses based on ANOVA F-test/Mann-Whitney test.
Abbreviations: TFD: Total fluid delivery; IVFT: Intravenous fluid therapy

Non-dialysed AKI participants (AKI-ND) received a significantly higher total cumulative (litres: p=0.005) and mean daily fluid delivery (L/d: p=0.01) compared to their dialysed (AKI-D) and normal renal function (NRF) counterparts. AKI-ND participants had a significantly higher mean daily crystalloid delivery compared to AKI-D and NRF participants (L/d: p<0.01) (Table 4-6).

Table 4-6 Total fluid delivery (TFD) and IV fluid therapy (IVFT) according to renal function

	Unit	NRF	N	AKI-ND	N	AKI-D	N	p-value
TFD								
Total cumulative	L	16.8 ± 4.7	40	21.3 ± 4.6	15	19.0 ± 3.6	16	0.005
Mean daily	L/d	3.0 ± 0.6	40	3.7 ± 0.7	15	3.1 ± 0.4	16	0.01
Mean daily	mL/kg/d	48.3 ± 11.6	40	56.1 ± 13.4	15	48.6 ± 8.0	16	0.11
Mean daily IVFT	L/d	1.0 ± 0.4	40	1.5 ± 0.7	15	0.8 ± 0.3	16	<0.01
Crystalloids	L/d	0.8 ± 0.4	39	1.1 ± 0.5	15	0.5 ± 0.2	16	<0.01
Colloids	L/d	0.2 ± 0.1	31	0.3 ± 0.2	13	0.2 ± 0.1	12	0.06
Blood products	L/d	0.1 ± 0.1	18	0.3 ± 0.4	11	0.3 ± 0.3	12	0.20
Contribution to TFD (%)								
IV fluid therapy	%	31.8 ± 11.2	40	39.6 ± 12.9		25.2 ± 9.0	16	0.003

Data are presented as mean ± SD. Statistical analyses are based on ANOVA F-test/Kruskal-Wallis test.

Abbreviations: IVFT: Intravenous fluid therapy; TFD: Total fluid delivery; NRF: Normal renal function; AKI-ND: Acute kidney injury with no dialysis; AKI-D: Acute kidney injury with dialysis; N: Sample size

4.4 Electrolyte delivery:

4.4.1 IV electrolyte supplementation

In total seventy (n=70) study participants received IV electrolyte supplementation. Figure 4-8 shows the type of IV electrolyte supplements (IVES) most often prescribed to the study participants.

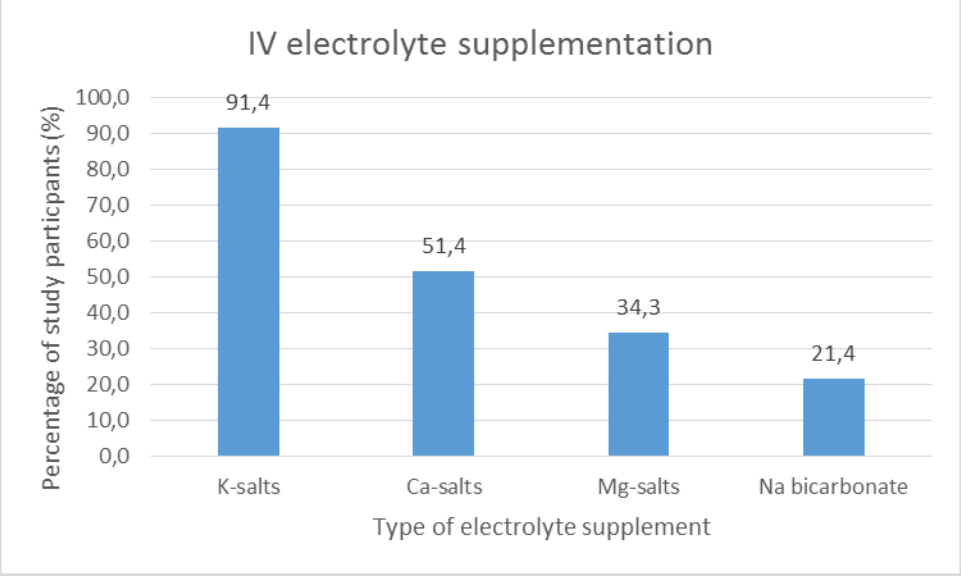

Figure 4-8 Percentage of study participants receiving IV electrolyte supplementation (n=70)

Potassium salts (i.e. potassium chloride or potassium phosphate) were prescribed to sixty-four (91.4%) of the seventy study participants who received IV electrolyte supplementation. Calcium- (i.e. calcium chloride or calcium gluconate), magnesium- (i.e. magnesium sulphate) and sodium bicarbonate salts (i.e. sodium bicarbonate 8.5%) were prescribed to thirty-six (51.4%), twenty-four (34.3%) and fifteen (21.4%) study participants respectively. Table 4-7 shows the dosing of the IVES that were most often prescribed to the study participants. This is based on observation, since the calculation of mean doses are not a true reflection of prescribed single doses.

Table 4-7 Often prescribed dosing of IV electrolyte supplements

	Indications	Dosing per single administration	
		Prescribed dose	Provides
Potassium chloride 15%	Hypokalemia	10 – 30ml (1.5 – 3g)	K^+ 20 – 60 mmol Cl^- 20 – 60 mmol
Potassium phosphate	Hypokalemia Hypophosphatemia	10 – 30ml (2.14 – 6.42g)	K^+ 20 - 60 mmol HPO_4^- 14 – 42 mmol
Calcium chloride 10%	Hypocalcemia	10ml (1g)	Ca^{2+} 6.8 mmol Cl^- 13.6 mmol
Calcium gluconate 10%	Hyperkalemia Hypocalcemia	10ml	Ca^{2+} 2.325 mmol
Magnesium sulphate	Hypomagnesemia Refractory hypokalemia	4ml (2g)	Mg^{2+} 8mmol
Sodium bicarbonate 8.5%	Metabolic acidosis	150ml	Na^+ 150 mmol

4.4.2 Total electrolyte delivery

Mean daily sodium and chloride delivery was 3.7 ± 1.2 and 3.6 ± 1.2mmol/kg/d respectively. This was more than double the maintenance requirement of 1 – 1.5 and 1.5mmol/kg/day respectively.[2] The greatest contributor was IVFT contributing 42% and 38% to total sodium and chloride delivery respectively. This was followed by the use of saline for the reconstitution and dilution of IV drugs which contributed a further 28% to both sodium and chloride delivery.

The mean daily potassium delivery of 1.3 ± 0.4mmol/kg/d was slightly higher than the maintenance requirement of 1mmol/kg/d. The greatest contributor to total potassium intake was EN with a mean contribution of 62%. This was followed by IV electrolyte supplementation which contributed a further 35% to total potassium delivery.

The mean daily magnesium delivery of 0.2 ± 0.1mmol/kg/d met the maintenance requirement of 0.1 – 0.2mmol/kg/d. The greatest contributor was once again EN contributing 88% to total magnesium delivery. The mean daily calcium and phosphate delivery of 0.4 ± 0.2 and 0.7 ± 0.4 mmol/kg/d exceeded the maintenance requirements of 0.1 – 0.2 and 0.2 – 0.5 mmol/kg/d respectively.[2] EN contributed 88% to total calcium delivery, whereas EN and the administration of fleet enemas contributed 93% to total phosphate delivery. Table 4-8 – table 4-13 provides a summary of sodium, potassium, chloride, calcium, magnesium and phosphate delivery according to the following:

(1) Cumulative delivery over entire study period (mmol)

(2) Mean daily delivery (mmol/d and mmol/kg/d)

(3) Breakdown according to route of delivery (IV, enteral and oral)

Table 4-8 Breakdown of total cumulative sodium delivery

Variables	N-size	Cumulative delivery (mmol)		% of total sodium delivery	
		Mean ± SD (median)	**Range**	**Mean ± SD (median)**	**Range**
TOTAL CUMULATIVE DELIVERY [A]	71	1347.3 ± 471.0 (1296.7)	428.6 – 2526.1	-	-
Mean daily delivery (mmol/d)	71	237.1 ± 72.4 (238.0)	100.5 – 384.7	-	-
Mean daily delivery (mmol/kg/d)	71	3.7 ± 1.2 (3.7)	1.6 – 6.4	-	-
BREAKDOWN ACCORDING TO ROUTE OF DELIVERY					
INTRAVENOUS	71	1053.7 ± 463.4 (981.9)	188.9 – 2194.9	76.9 ± 13.9 (76.6)	42.8 – 100.0
Fluid therapy	69	578.6 ± 323.8 (497.9)	120.1 – 1379.2	41.6 ± 15.5 (40.4)	11.2 – 79.2
Crystalloid	69	432.8 ± 286.4 (347.1)	10.5 – 1337.6		
Colloid	56	179.7 ± 132.2 (154.0)	38.5 – 500.5		
Drug administration[B]	71	373.1 ± 218.5 (336.9)	8.9 – 1160.6	27.7 ± 13.0 (25.7)	1.1 – 56.9
Flushing of IV lines	71	78.4 ± 22.8 (77.8)	27.3 – 155.2	6.4 ± 2.7 (5.9)	3.2 – 17.2
Electrolyte supplementation[C]	15	175.8 ± 188.5 (109.0)	27.4 – 602.2	10.2 ± 9.0 (5.3)	2.3 – 30.0
Nutrition	5	39.8 ± 46.0 (17.4)	8.1 – 118.0	2.2 ± 2.5 (1.5)	0.5 – 6.5
ENTERAL	68	306.0 ± 182.8 (282.9)	39.9 – 813.6	24.1 ± 13.3 (24.5)	1.9 – 57.2
Nutrition	67	277.4 ± 175.7 (246.7)	16.2 – 813.6	21.9 ± 13.0 (19.4)	1.3 – 57.2
Fleet enema	27	82.3 ± 61.9 (64.4)	16.1 – 289.8	-	-
ORAL [D]	7	4.7 ± 3.6 (4.4)	0.1 – 11.0	0.3 ± 0.2 (0.3)	0 – 0.5

Data are presented as mean ± SD (median) and ranges.

[A]Total cumulative delivery: Total cumulative sodium delivery (mmol) over total study hours.

[B]Drug administration: Sodium derived from fluids used for reconstitution and dilution purposes, as well as sodium-containing blood derivatives; i.e. *polygam* and *hemosolvex*

[C]Electrolyte supplementation: Sodium bicarbonate 8.5%

[D]Oral: Nutrition (e.g. sipfeeds)

Table 4-9 Breakdown of total cumulative potassium delivery

Variables	N-size	Cumulative delivery (mmol)		% of total potassium delivery	
		Mean ± SD (median)	Range	Mean ± SD (median)	Range
TOTAL CUMULATIVE DELIVERY[A]	71	462.8 ± 168.8 (446.1)	133.9 – 850.4	-	-
Mean daily delivery (mmol/d)	71	81.7 ± 26.3 (81.5)	22.0 – 164.8	-	-
Mean daily delivery (mmol/kg/d)	71	1.3 ± 0.4 (1.3)	0.4 – 2.4	-	-
BREAKDOWN ACCORDING TO ROUTE OF DELIVERY					
INTRAVENOUS	70	158.7 ± 116.1 (139.7)	4.0 – 516.2	35.7 ± 25.2 (30.3)	0.7 – 100
Fluid therapy	66	12.8 ± 9.4 (10.4)	0.4 – 49.2	3.1 ± 2.5 (2.6)	0.1 – 13.5
Crystalloid	66	12.8 ± 9.4 (10.4)	0.4 – 49.2	±	±
Colloid	2	1.2 ± 1.6 (1.2)	0.1 – 2.3	±	±
Electrolyte supplementation[B]	64	158.1 ± 105.2 (140.0)	20.0 – 500.0	34.6 ± 21.1 (29.8)	4.7 – 96.1
Nutrition	5	29.6 ± 34.1 (12.9)	6.0 – 87.5	15.9 ± 27.7 (3.6)	1.1 – 65.4
ENTERAL	67	323.7 ± 139.9 (306.1)	30.4 – 672.0	68.5 ± 20.2 (71.6)	9.9 - 100
Nutrition	67	292.4 ± 137.3 (292.1)	15.8 – 609.7	61.7 ± 21.4 (64.3)	4.4 – 100.0
Mist KCl	35	57.4 ± 38.9 (48.0)	16.0 – 192.0	-	-
ORAL [C]	6	10.0 ± 14.6 (3.3)	1.5 – 38.6	2.0 ± 3.0 (0.8)	0.2 – 7.9

Data are presented as mean ± SD (median) and ranges.

[A]Total cumulative delivery: Total cumulative potassium delivery (mmol) over total study hours.

[B]Electrolyte supplementation: Potassium salts (Potassium chloride 15% and -phosphate)

[C]Oral: Nutrition (e.g. sipfeeds) and Mist KCl supplementation

Table 4-10 Breakdown of total cumulative chloride delivery

Variables	N-size	Cumulative delivery (mmol)		% of total chloride delivery	
		Mean ± SD (median)	Range	Mean ± SD (median)	Range
TOTAL CUMULATIVE DELIVERY[A]	71	1307.1 ± 436.5 (1270.4)	388.0 – 2458.1	-	-
Mean daily delivery (mmol/d)	71	230.6 ± 68.4 (220.3)	92.2 – 373.6	-	-
Mean daily delivery (mmol/kg/d)	71	3.6 ± 1.2 (3.3)	1.5 – 7.1	-	-
BREAKDOWN ACCORDING TO ROUTE OF DELIVERY					
INTRAVENOUS	71	1102.5 ± 448.1 (1001.8)	208.9 – 2458.1	82.8 ± 11.1 (83.7)	41.7 – 100
Fluid therapy	69	524.6 ± 296.6 (445.0)	120.1 – 1266.5	38.4 ± 13.7 (38.3)	10.0 – 71.5
Crystalloid	69	379.1 ± 259.3 (293.7)	9.0 – 1228.0	-	-
Colloid	56	179.2 ± 132.1 (154.0)	38.5 – 500.5	-	-
Drug administration[B]	71	372.2 ± 217.3 (336.9)	8.9 – 1160.6	27.8 ± 12.4 (28.1)	1.8 – 56.5
Flushing of lines	71	78.4 ± 22.8 (77.8)	27.3 – 155.2	6.5 ± 2.8 (6.0)	3.1 – 19.5
Electrolyte supplementation[C]	65	150.9 ± 96.8 (140.0)	13.6 – 500.0	11.9 ± 7.3 (10.8)	1.7 – 39.4
Nutrition	5	57.8 ± 66.8 (25.2)	11.7 – 171.2	3.3 ± 4.0 (2.2)	0.7 – 10.3
ENTERAL	67	216.1 ± 114.6 (193.7)	15.6 – 466.5	18.2 ± 10.5 (16.5)	0.8 – 58.3
Nutrition	67	184.8 ± 110.7 (167.3)	15.6 – 466.5	15.5 ± 10.1 (15.4)	0.8 – 58.3
Mist KCl	35	59.9 ± 39.6 (48.0)	16.0 – 192.0	-	-
ORAL[D]	6	9.1 ± 13.9 (2.5)	0.8 – 36.2	0.7 ± 1.1 (0.2)	0.1 – 2.8

Data are presented as mean ± SD (median) and ranges.

[A]Total cumulative delivery: Total cumulative chloride delivery (mmol) over total study hours.

[B]Drug administration: Chloride derived from fluids used for reconstitution and dilution purposes (excluding chloride-containing drugs)

[C]Electrolyte supplementation: Potassium chloride 15% & Calcium chloride 10%

[D]Oral: Nutrition (e.g. sipfeeds) and Mist KCl supplementation

Table 4-11 Breakdown of total cumulative calcium delivery

Variables	N-size	Cumulative delivery (mmol)		% of total calcium delivery	
		Mean ± SD (median)	Range	Mean ± SD (median)	Range
TOTAL CUMULATIVE DELIVERY[A]	71	149.5 ± 78.6 (156.6)	0 – 314.4	-	-
Mean daily delivery (mmol/d)	71	26.2 ± 13.0 (27.5)	0 – 57.5	-	-
Mean daily delivery (mmol/kg/d)	71	0.4 ± 0.2 (0.4)	0 – 0.8	-	-
BREAKDOWN ACCORDING TO ROUTE OF DELIVERY					
INTRAVENOUS	54	9.3 ± 7.0 (7.2)	0.2 – 31.3	13.7 ± 21.4 (6.1)	0.1 - 100
Fluid therapy	36	4.2 ± 3.7 (2.7)	0.1 – 14.9	6.9 ± 14.7 (2.0)	0.1 – 80.1
Crystalloid	36	4.2 ± 3.7 (2.7)	0.1 – 14.9	-	-
Colloid	1	0.1	-	-	-
Electrolyte supplementation[B]	36	9.4 ± 6.1 (6.8)	2.3 – 29.5	11.6 ± 13.2 (6.8)	1.1 – 63.6
Nutrition	5	2.6 ± 3.0 (1.1)	0.5 – 7.6	15.1 ± 18.6 (6.4)	0.5 – 45.5
ENTERAL[C]	67	150.6 ± 75.4 (155.1)	7.0 – 314.1	88.4 ± 12.9 (96.3)	32.7 - 100
ORAL[D]	6	4.0 ± 4.1 (2.8)	0.5 – 10.2	4.5 ± 5.5 (3.0)	0.2 – 15.0

Data are presented as mean ± SD (median) and ranges.

[A]Total cumulative delivery: Total cumulative calcium delivery (mmol) over total study hours.

[B]Electrolyte supplementation: Calcium chloride 10%, calcium gluconate 10%

[C]Enteral: EN

[D]Oral: Nutrition (e.g. sipfeeds)

Table 4-12 Breakdown of total cumulative magnesium delivery

Variables	N-size	Cumulative delivery (mmol)		% of total energy	
		Mean ± SD (median)	**Range**	**Mean ± SD (median)**	**Range**
TOTAL CUMULATIVE DELIVERY[A]	71	68.9 ± 30.7 (65.6)	6.4 – 138.6	-	-
Mean daily delivery (mmol/d)	71	12.0 ± 4.7 (12.6)	1.0 – 21.1	-	-
Mean daily delivery (mmol/kg/d)	71	0.2 ± 0.1 (0.2)	0.0 – 0.3	-	-
BREAKDOWN ACCORDING TO ROUTE OF DELIVERY					
INTRAVENOUS	56	9.1 ± 10.2 (5.7)	0.2 – 48.0	21.0 ± 28.5 (7.5)	0.1 - 100
Fluid therapy[B]	50	3.1 ± 2.3 (2.6)	0.2 – 9.0	7.7 ± 10.4 (3.7)	0.1 – 49.8
Electrolyte supplementation[C]	24	13.3 ± 11.8 (8.0)	4.0 – 48.0	26.2 ± 19.3 (21.9)	3.8 – 68.0
Nutrition	5	5.1 ± 5.9 (2.2)	1.0 – 15.2	26.7 ± 32.0 (8.8)	1.5 – 79.2
ENTERAL[D]	67	65.3 ± 28.6 (64.9)	3.4 – 129.1	88.1 ± 17.9 (95.9)	28.0 - 100
ORAL[E]	6	1.2 ± 1.1 (1.1)	0.1 – 2.5	3.0 ± 2.9 (2.5)	0.1 – 6.6

Data are presented as mean ± SD (median) and ranges.

[A]Total cumulative delivery: Total cumulative calcium delivery (mmol) over total study hours.

[B]Fluid therapy: Crystalloids

[C]Electrolyte supplementation: Magnesium sulphate 50%

[D]Enteral: EN

[E]Oral: Nutrition (e.g. sipfeeds)

Table 4-13 Breakdown of total cumulative phosphate delivery

Variables	N-size	Cumulative delivery (mmol)		% of total energy	
		Mean ± SD (median)	Range	Mean ± SD (median)	Range
TOTAL CUMULATIVE DELIVERY[A]	71	241.1 ± 165.4 (197.8)	44.2 – 999.7	-	-
Mean daily delivery (mmol/d)	71	42.2 ± 27.1 (33.4)	7.2 – 154.8	-	-
Mean daily delivery (mmol/kg/d)	71	0.7 ± 0.4 (0.5)	0.1 – 2.1	-	-
BREAKDOWN ACCORDING TO ROUTE OF DELIVERY					
INTRAVENOUS	20	51.8 ± 33.2 (43.5)	8.2 – 140.0	39.2 ± 32.7 (27.8)	6.6 - 100
Electrolyte supplementation[B]	10	65.8 ± 37.4 (63.0)	14.0 – 140.0	37.4 ± 15.1 (31.2)	16.7 – 62.2
Nutrition	14	27.0 ± 12.5 (28.5)	8.2 – 54.9	29.2 ± 29.1 (16.1)	6.6 – 100
ENTERAL[C]	68	236.2 ± 165.8 (199.8)	20.3 – 999.7	92.7 ± 16.2 (100)	29.4 - 100
ORAL[D]	6	3.3 ± 3.2 (3.0)	0.3 – 7.8	1.8 ± 2.3 (1.0)	0 – 6.2

Data are presented as mean ± SD (median) and ranges.

[A]Total cumulative delivery: Total cumulative phosphate delivery (mmol) over total study hours.

[B]Electrolyte supplementation: Potassium phosphate

[C]Enteral: EN and fleet enemas

[D]Oral: Nutrition (e.g. sipfeeds)

4.5 Contribution of non-nutritional fluids to total fluid and electrolyte delivery

Total fluid, sodium and chloride delivery were mostly derived from non-nutritional sources (60%, 79% and 85% respectively), whereas NT was the greatest contributor to total potassium, calcium, magnesium and phosphate delivery (60%, 88%, 85% and 75% respectively). Table 4-14 and Figure 4-9 show the mean percentage contribution of non-nutritional fluids versus NT to total fluid and electrolyte delivery across all study participants (n=71). In this study unit the contribution of NT to electrolyte delivery was influenced by the routine use of electrolyte-free PN regimens. NT may therefore be a greater contributor to electrolyte delivery in units where PN is not restricted to the use of electrolyte-free PN regimens.

Non-nutritional sodium sources included sodium-containing crystalloids, HES, blood derivatives (i.e. hemosolvex, polygams), sodium bicarbonate supplementation and the administration of fleet enemas. Non-nutritional chloride sources included chloride-containing crystalloids, HES, polygam infusions and potassium chloride supplementation. Interestingly, a significant correlation was found between severity of illness (APACHE II score) on admission to ICU and the percentage contribution of IVFT to total chloride delivery (n=69, spearman R: -0.246754, p=0.040956). Hence the higher the APACHE II score, the lower the percentage contribution of IVFT to total chloride delivery. Despite potassium salts being the most commonly prescribed IVES, NT was still the greatest contributor to total potassium delivery (60%).

Important to take note is that the electrolyte content of the prescribed drugs (e.g. sodium-containing antimicrobial agents) were not taken into account and could have further contributed to total electrolyte intake.

Table 4-14 Contribution of non-nutritional fluids versus NT to fluid and electrolyte delivery

	% Non-nutritional sources		**% Nutrition therapy**	
Fluid	59.8 ± 12.1 (58.2)	31.5 – 87.8	40.2 ± 12.1 (41.8)	12.2 – 68.5
Sodium	79.2 ± 13.4 (81.6)	42.8 – 100	20.8 ± 13.4 (18.4)	0 – 57.2
Potassium	40.5 ± 23.8 (36.3)	0 – 100	59.5 ± 23.8 (63.7)	0 – 100
Chloride	85.1 ± 10.2 (86.7)	41.7 – 100	14.9 ± 10.2 (13.3)	0 – 58.3
Calcium	12.2 ± 21.4 (3.8)	0 - 100	87.8 ± 21.6 (96.2)	0 – 100
Magnesium	14.7 ± 22.9 (4.2)	0 – 100	85.3 ± 22.9 (95.8)	0 – 100
Phosphate	25.2 ± 29.9 (0)	0 – 91.3	74.8 ± 29.9 (100)	8.7 - 100

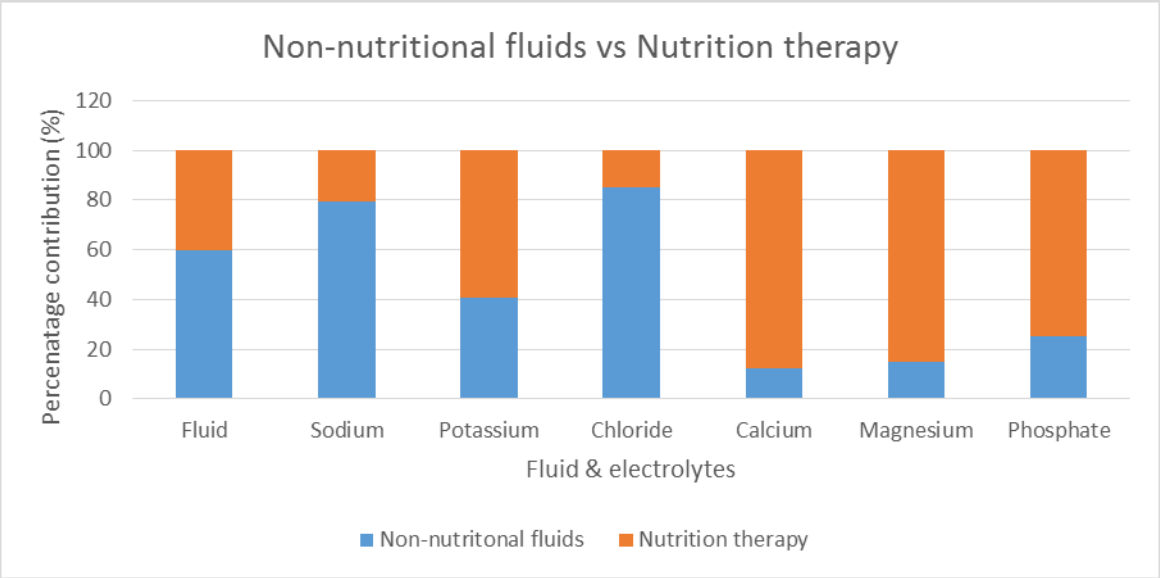

Figure 4-9 Contribution of NT versus non-nutritional fluids to total fluid and electrolyte delivery

4.6 Energy and macronutrient delivery

4.6.1 Nutrition therapy

Nutrition therapy (NT) was most commonly provided via the enteral route: Fifty-four (76.1%) study participants were fed exclusively via the enteral route, three (4.2%) received combined EN and oral nutrition, ten (14.1%) received a combination of EN and PN, while only four patients (5.6%) received sole PN (Table 4-15). Patients who received a combination of EN and oral nutrition were initially fed orally and enteral nutrition (EN) initiated at a later stage due to; (1) inadequate oral nutrition or (2) no longer able to take feeds orally (e.g. post-intubation). Hence a total of fifty-seven study participants (80.3%) were fed via the enteral route without the use of supplemental PN.

NT was initiated within 14.5 ± 14.1 hours (median 11, range 0 – 69) after admission to ICU. Table 4-16 shows a breakdown of the time to initiation of NT according to the primary admission diagnosis. There was a non-significant trend (p=0.23) towards a longer nil per os (NPO) period in gastrointestinal patients compared to the other primary admission diagnoses (24 hours versus 12 – 15 hours).

The average duration of NT; i.e. from initiation of NT until study exit was 5.1 days (median 5.4, range 3.0 – 6.6 days) (Table 4-15). A significant association was found between study participants' age and the time (hours) to initiation of NT (n=71, Spearman R=0.24, p=0.04). This indicates that NT was initiated earlier in older patients. There was no significant association between the time

(hours) to initiation of NT and gender, nutritional status (BMI) on admission to ICU, admission category or primary admission diagnosis.

Table 4-15 Breakdown of nutritional parameters

Variables	Unit	Mean ± SD (median)	Range
Study duration[A]			
	Hours	136.9 ± 25.3 (152.0)	83.0 – 168.0
	Days	5.7 ± 1.1 (6.3)	3.5 – 7.0
Time to initiation of NT			
	Hours	14.5 ± 14.1 (11.0)	0 – 69.0
NT duration[B]			
	Hours	122.5 ± 24.8 (129.0)	71.0 – 158.0
	Days	5.1 ± 1.0 (5.4)	3.0 – 6.6
Route of NT			
EN only	n (%)	54 (76.1)	
EN & Oral		3 (4.2)	
PN only		4 (5.6)	
PN & EN		10 (14.1)	
Calculated requirements			
Weight used for calculations	kg	64.9 ± 8.5 (65.0)	46.0 – 92.0

Data are presented as N (%), mean ± SD (median) and ranges.

[A]Study duration: Time from admission until study exit (hours/days)

[B]NT duration: Time from initiation of NT until study exit (hours/days)

Abbreviations: NT: Nutrition therapy, EN: Enteral nutrition; PN: Parenteral nutrition

.

Table 4-16 Hours to initiation of NT according to primary admission diagnosis (p=0.23)

Primary admission diagnosis	n-size	Mean ± SD (median)	Range
All	71	14.5 ± 14.1 (11.0)	0 – 69
Gastrointestinal	10	24.2 ± 18.1 (25.5)	0 – 65
Sepsis	20	14.9 ± 16.2 (10.5)	1 – 69
Neurological	13	11.5 ± 12.0 (10.0)	1 – 43
Respiratory	17	12.5 ± 11.0 (9.0)	2 – 45
Other	11	11.5 ± 10.2 (10.0)	1 – 38

Data are presented as means ± SD (median) and ranges. Statistical analyses based on ANOVA F-test.

4.6.2 Energy parameters

The mean daily energy delivered was 1613 ± 380kCal (25.1kCal/kg), meeting 93.6 ± 17.7% of the mean target range of 25.4 – 28.6kCal/kg/d. The mean cumulative energy balance was -674.0 ± 1866.1kCal. NNES contributed 10.1 ± 7.5% to total energy delivered (Table 4-17).

Table 4-17 Breakdown of energy delivery parameters

Variables	Mean ± SD (median)	Range
CALCULATED ENERGY TARGET		
Minimum target		
Total kCal[A]	9431.7 ± 2432.2 (9464.6)	4604.2 – 15706.7
kCal/kg/d	25.4 ± 3.0 (25.0)	20.0 – 40.0
Maximum target		
Total kCal	10594.2 ± 2663.6 (10875.0)	4958.3 – 17670.0
kCal/kg/d	28.6 ± 3.5 (28.5)	24.8 – 45.0
ACTUAL ENERGY DELIVERY		
Total kCal	9199.2 ± 2826.3 (9169.2)	3466.8 – 16584.9
Mean kCal/d	1612.6 ± 379.8 (1642.0)	740.4 – 2618.7
Mean kCal/kg/d	25.1 ± 6.1 (25.7)	9.7 – 42.2
ACTUAL DELIVERY VERSUS TARGET		
Mean percent target[B]	93.6 ± 17.7 (100)	39.41 – 133.0
Cumulative balance	-674.0 ± 1866.1 (0)	-7231.3 – 2835.6
CONTRIBUTION OF NNES		
% Nutrition therapy	89.9 ± 7.477 (91.793)	70.860 – 100
% Non-nutritional sources	10.1 ± 7.477 (8.207)	0.00 – 29.14

Data are presented as mean ± SD (median) and ranges.

[A]Total kCal: Cumulative energy delivery over entire study period

[B]Mean percent target: Refer to section 3.8.3 for calculation of mean percent target

Abbreviations: kCal: kilocalories; NNES: Non-nutritional energy sources

Females (n=36) had a significantly lower mean daily energy intake (kCal/d: 1491.5 ± 353.7 vs 1737.1 ± 369.8, p<0.01) compared to males (n=35). Mean daily energy delivery was not significantly influenced by the APACHE II score on admission to ICU. A significant negative correlation was found between nutritional status (BMI) on admission to ICU and mean daily energy delivery expressed as kCal/kg/d (n=71, R= -0.32925, p=0.005052). Hence the higher the BMI, the lower the weight-based mean daily energy delivery. Furthermore, a significant negative correlation was found between the time (hours) to initiation of NT and mean daily energy delivery (kCal/d:

n=71, R= -0.35386, p=0.002467; kCal/kg/d: n=71, R=-0.27066, p=0.022437). Hence the longer it takes to initiate NT, the lower the overall mean daily energy delivery.

4.6.3 Macronutrient breakdown

Table 4-18 shows the total carbohydrate, protein and lipid delivery derived from both nutritional and non-nutritional sources. Total energy delivery (TED) was mostly derived from carbohydrate sources (51%), while lipid and protein sources contributed a further 31% and 18% respectively. The mean daily carbohydrate and lipid delivery (g/kg/d) fell within the recommended daily weight-based range of 3 – 5g/kg and 0.7 – 1.5g/kg respectively.[13,66,80] The mean daily protein delivery of 1.1g/kg/d was below the general ICU recommendation of 1.2 – 2.0 g/kg per day.[67]

Table 4-18 Macronutrient breakdown of energy delivery

Variables	N-size	Mean ± SD (median)	Range
CARBOHYDRATE DELIVERY			
Total delivery (g)	71	1164.0 ± 372.1 (1169.9)	473.8 – 2096.8
Mean daily delivery (g/d)	71	203.5 ± 49.1 (207.2)	105.3 – 312.6
Mean daily delivery (g/kg/d)	71	3.2 ± 0.8 (3.2)	1.6 – 5.2
% of total energy		50.9 ± 6.4 (50.9)	33.6 – 66.3
PROTEIN DELIVERY			
Total delivery (g)	71	406.8 ± 143.9 (401.0)	119.8 – 853.0
Mean daily delivery (g/d)	71	71.5 ± 21.5 (75.0)	20.8 – 134.7
Mean daily delivery (g/kg/d)	71	± 0.3 (1.1)	0.3 – 2.2
% of total energy		17.6 ± 2.9 (18.0)	11.3 – 25.3
LIPID DELIVERY			
Total delivery (g)	71	324.0 ± 116.5 (319.7)	77.1 – 607.0
Mean daily delivery (g/d)	71	56.9 ± 17.9 (57.5)	16.1 – 108.2
Mean daily delivery (g/kg/d)	71	0.9 ± 0.3 (0.9)	0.2 – 1.5
% of total energy		31.4 ± 5.6 (30.9)	19.3 – 45.4

Data are presented as mean ± SD (median) and ranges.

4.6.4 Protein parameters

Table 4-19 shows the mean daily protein target range, actual protein delivery, mean percent target and cumulative protein balance for all study participants (n=71). Mean daily protein delivery was 72 ± 22g (1.1g/kg), meeting 82.8 ± 19.9% of the mean target range of 1.3 – 1.5g/kg/d. The mean cumulative protein balance was -86.0 ± 106.9g.

Contrary to energy delivery, there were no gender differences in overall protein delivery. Mean daily protein delivery was not significantly influenced by the APACHE II score on admission to ICU. A significant negative correlation was found between nutritional status (BMI) on admission to ICU and mean daily protein delivery expressed as g/kg/d (n=71, R=-0.256313, p=0.030960). Hence the higher the BMI, the lower the weight-based mean daily protein delivery (g/kg/d).

As with energy delivery, a significant association was found between the time (hours) to initiation of NT and mean daily protein delivery (g/d: n=71, R= -0.344892, p=0.003225; g/kg/d: n=71, R=-0.298222, p=0.011536). Hence the longer it takes to initiate NT, the lower the overall mean daily protein delivery. This was similar to energy delivery and emphasizes the need to initiate feeds early if possible.

Table 4-19 Breakdown of protein delivery parameters

Variables	Mean ± SD (median)	Range
CALCULATED PROTEIN TARGET		
Minimum target		
Total grams[A]	475.6 ± 121.2 (480.0)	240.0 – 785.4
g/kg/d	1.3 ± 0.2 (1.2)	0.8 – 2.0
Maximum target		
Total grams	560.0 ± 143.7 (556.8)	300.0 – 981.7
g/kg/d	1.5 ± 0.2 (1.5)	1.2 – 2.5
ACTUAL PROTEIN DELIVERY		
Total grams	406.759 ± 143.923 (401.000)	119.770 – 852.96
Mean g/d	71.543 ± 21.505 (75.035)	20.830 – 134.678
Mean g/kg/d	1.114 ± 0.341 (1.115)	0.331 – 2.172
ACTUAL DELIVERY VERSUS TARGET		
Mean percent target[B]	82.751 ± 19.857 (88.589)	23.510 – 103.341
Cumulative balance	-85.991 ± 106.907 (-45.015)	-546.275 – 11.725

Data are presented as mean ± SD (median) and ranges.

[A]Total grams: Cumulative protein delivery over entire study period

[B]Mean percent target: Refer to section 3.8.3. for calculation of mean percent target

Abbreviations: g: grams

4.7 Contribution of non-nutritional IV fluids to energy and macronutrient delivery

4.7.1 Energy

On average NT contributed 89.9 ± 7.5 % to TED, whereas the remaining 10.1 ± 7.5 % was derived from non-nutritional IV fluids prescribed by the ICU physician or administered as part of standard therapeutic ICU protocols (Table 4-17). Figure 4-10 shows the mean percentage contribution of NNES to TED across all study participants (n=71). The majority of participants (73%) received more than 5% of their total energy intake from NNES.

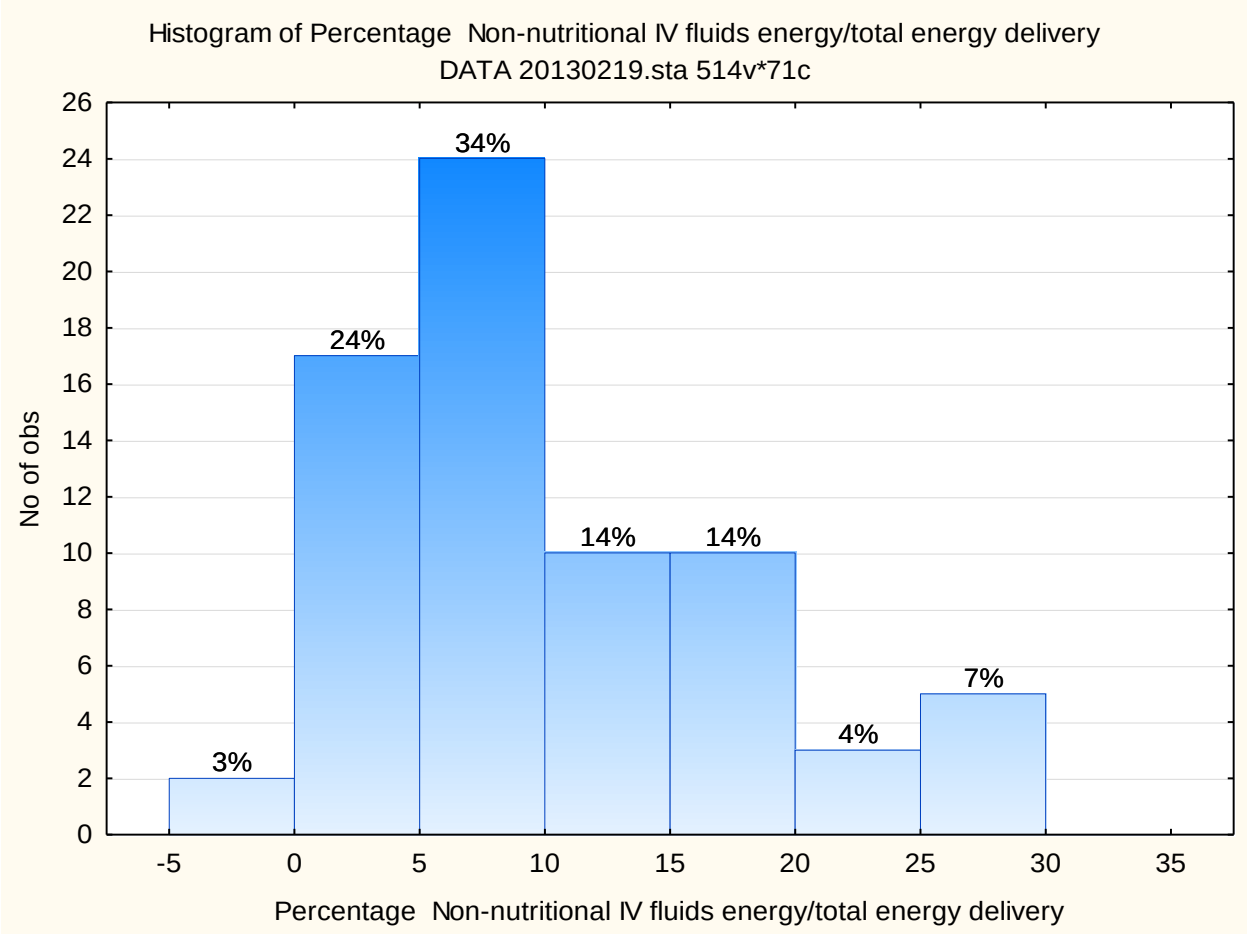

Figure 4-10 Percentage contribution of non-nutritional IV fluids to total energy delivery

Table 4-20 shows the mean daily energy delivery from all NNES. On average, NNES provided 156kCal/d. IVFT in the form of dextrose-containing crystalloids and starch-containing colloids (i.e. HES) provided 102kCal/d (n=65). Energy delivery via polygam infusions (sucrose used as stabilizer) prescribed in the treatment of Guillian-bare syndrome (n=3) provided 101kCal/d. Propofol, a lipid-based sedative used in the treatment of status epilepticus (n=7), provided approximately 139kCal/d. The use of 5% dextrose water in the dilution of IV drugs, a routine

practice seen in hypernatraemic patients and in the dilution of certain medications (Amiodarone, Amphotericin B), provided approximately 42kCal/d. Furthermore the use of 50% dextrose water in the treatment of hypoglycaemia and hyperkalemia provided an additional 36kCal/d.

Table 4-20 Daily energy contribution (kCal/d) of different NNES

Variables	n-size	Mean ± SD (median)	Range
All NNES	*71*	*156.3 ± 114.2 (133.0)*	*0 – 561.3*
Crystalloids	45	85.3 ± 63.2 (65.6)	5.1 – 258.9
Colloids (HES)	56	49.8 ± 35.9 (41.3)	8.9 – 135.8
Polygam	3	101.3 ± 54.6 (97.8)	48.5 – 157.5
Propofol	7	139.0 ± 120.8 (88.2)	31.2 – 316.6
IV drug dilution	41	41.9 ± 30.0 (37.4)	4.5 – 112.2
50% dextrose water	41	36.1 ± 25.1 (29.2)	6.1 – 109.8

Data are presented as mean ± SD (ranges).

Abbreviations: HES: Hydroxy-ethyl starch

Table 4-21 shows a detailed breakdown of energy delivery according to the different nutritional and non-nutritional energy sources. Non-nutritional energy delivery were mostly derived from carbohydrate sources, i.e. dextrose via fluid therapy crystalloids (5.4% to TED), dextrose via drug dilution (2.9% to TED), starch via HES infusion (3.5% to TED), sucrose via polygam infusion (4.9% to TED) and dextrose administered in the treatment of hypoglycemia and hyperkalemia (2.3% to TED). Energy delivery from non-nutritional protein sources were negligible since IV albumin infusion was prescribed to only one study participant (n=1). Energy delivery from non-nutritional lipid sources was derived from the IV infusion of propofol, contributing 7.2% to TED (n=7).

Table 4-21 Breakdown of energy delivery according to nutritional and non-nutritional sources

Variables	N-size	Cumulative delivery (kCal)		% of TED	
		Mean ± SD (median)	Range	Mean ± SD (median)	Range
CONTRIBUTION NON-NUTRITIONAL SOURCES					
% Nutrition therapy	71	-	-	89.9 ± 7.5 (91.8)	70.9 – 100.0
% NNES	71	-	-	10.1 ± 7.5 (8.2)	0.00 – 29.1
NUTRITION THERAPY BREAKDOWN		-	-		
Intravenous	16	4995.6 ± 3081.7 (4273.7)	430.7 – 10000.0	58.8 ± 32.1 (68.8)	2.6 – 96.4
Enteral	67	7584.7 ± 3364.0 (7657.4)	423.5 – 14385.5	81.0 ± 23.2 (88.9)	4.0 – 100.0
Oral	7	270.8 ± 188.0 (294.9)	41.3 – 500.0	2.9 ± 2.1 (3.3)	0.3 – 5.8
NON-NUTRITIONAL SOURCES BREAKDOWN					
Carbohydrate sources					
Dextrose via crystalloid infusion	45	496.9 ± 380.9 (409.2)	28.6 – 1628.7	5.4 ± 3.9 (4.2)	0.3 – 13.4
Dextrose via IV drug dilution	41	236.6 ± 169.5 (226.1)	22.0 – 648.9	2.9 ± 2.2 (2.3)	0.3 – 8.0
Starch via HES infusion	56	278.1 ± 205.5 (240.0)	60.0 – 780.0	3.5 ± 3.0 (2.3)	0.4 – 12.7
Sucrose via Polygam infusion	3	556.6 ± 213.6 (655.9)	311.5 – 702.5	4.9 ± 2.0 (4.7)	3.1 – 7.0
Dextrose via other routine practices[A]	41	207.3 ± 151.0 (160.0)	40.0 – 700.0	2.3 ± 1.9 (1.7)	0.3 – 9.4
Protein sources					
Albumin via Albusol infusion	1	184.0	-	1.644	-
Lipid sources					
Lipid via Propofol infusion	7	735.2 ± 635.2 (540.0)	117.0 – 1990.8	7.2 ± 6.6 (3.8)	1.9 – 18.1

Data are presented as mean ± SD (median) and ranges.

[A]Dextrose via other routine practices: 50% Dextrose water in the treatment of hyperkalemia and hypoglycemia

Abbreviations: HES: Hydroxy-ethyl starch

4.7.2 Carbohydrates

On average, carbohydrate containing IV fluids contributed 18% to total cumulative carbohydrate delivery. Table 4-22 shows a breakdown of total carbohydrate (CHO) delivery according to nutritional and non-nutritional sources. Total carbohydrate delivery refers to the cumulative carbohydrate delivery over the entire study period, i.e. from ICU admission until study exit.

4.7.3 Protein

The overall contribution of NNES to total protein delivery was negligible. Only one study participant (n=1) received additional protein from an IV albumin infusion and was therefore not considered for statistical analyses. IV glutamine administration (n=16) was considered a component of NT and was mostly derived from glutamine-containing parenteral nutrition regimens (n=13). Only three participants (n=3) received glutamine supplementation in the form of dipeptiven. Table 4-23 shows a breakdown of total protein delivery according to nutritional and non-nutritional sources. Total protein delivery refers to the cumulative protein delivery over the entire study period, i.e. from ICU admission until study exit.

4.7.4 Lipid

Propofol, the lipid-based sedative used in the treatment of status epilepticus, contributed 18% to total lipid delivery (n=7). Table 4-24 shows a breakdown of total lipid delivery according to nutritional and non-nutritional sources. Total lipid delivery refers to the cumulative lipid delivery over the entire study period, i.e. from ICU admission until study exit.

Table 4-22 Breakdown of carbohydrate delivery according to nutritional and non-nutritional sources

Variables	N-size	Cumulative delivery (grams)		% of total carbohydrate delivery	
		Mean ± SD (median)	Range	Mean ± SD (median)	Range
CONTRIBUTION NON-NUTRITIONAL SOURCES					
% Non-nutritional sources	71	-	-	17.6 ± 12.4 (14.6)	0 – 46.4
% Nutrition therapy	71	-	-	82.4 ± 12.4 (85.4)	53.6 - 100
NUTRITION THERAPY BREAKDOWN					
Intravenous	14	611.4 ± 335.3 (616.5)	194.4 – 1213.9	57.4 ± 28.1 (60.5)	15.8 – 93.8
Enteral	67	865.3 ± 403.0 (813.0)	57.0 – 1731.9	75.1 ± 22.6 (81.4)	5.2 - 100
Oral	7	28.4 ± 18.5 (24.8)	6.8 – 50.0	2.2 ± 1.3 (2.2)	0.5 – 3.9
NON-NUTRITIONAL SOURCES BREAKDOWN					
Dextrose via crystalloids	45	124.4 ± 95.0 (102.3)	7.2 – 407.2	10.1 ± 6.9 (8.6)	0.6 – 26.9
Dextrose via drug dilution	41	59.2 ± 42.4 (56.5)	5.5 – 162.2	5.3 ± 3.7 (4.4)	0.6 – 13.9
Starch via HES infusion	56	69.5 ± 51.4 (60.0)	15.0 – 195.0	6.5 ± 5.3 (4.8)	0.7 – 19.9
Sucrose via Polygam infusion	3	139.2 ± 53.4 (164.0)	77.9 – 175.6	9.8 ± 4.8 (7.8)	6.3 – 15.3
Dextrose via other routine practices[A]	41	51.8 ± 37.7 (40.0)	10.0 – 175.0	5.1 ± 5.6 (3.3)	0.6 – 33.0

Data are presented as mean ± SD (median) and ranges.

[A]Dextrose via other routine practices: 50% Dextrose water in the treatment of hyperkalemia and hypoglycemia

Abbreviations: CHO: Carbohydrates; HES: Hydroxy-ethyl starch

Table 4-23 Breakdown of protein delivery according to nutritional and non-nutritional sources

Variables	N-size	Cumulative delivery (grams)		% of total protein	
		Mean ± SD (median)	Range	Mean ± SD (median)	Range
CONTRIBUTION NON-NUTRITIONAL SOURCES					
% Nutrition therapy	71	-	-	99.9 ± 0.9 (100.0)	92.1 – 100
% Non-nutritional sources	71	-	-	0.1 ± 0.9 (0)	0 – 7.9
NUTRITION THERAPY ENERGY BREAKDOWN					
Intravenous[A]	16	242.7 ± 126.3 (190.8)	79.2 – 463.9	68.4 ± 30.6 (76.3)	12.6 - 100
Glutamine[B]	16	47.1 ± 38.0 (29.3)	3.6 – 118.4	12.5 ± 10.8 (11.7)	1.7 – 49.1
Enteral	67	371.1 ± 174.3 (375.5)	16.8 – 745.3	89.2 ± 25.6 (100)	4.1 - 100
Oral	7	12.1 ± 8.1 (14.0)	0.6 – 20.0	3.1 ± 2.4 (3.5)	0.1 – 6.5
NON-NUTRITIONAL ENERGY BREAKDOWN					
Albumin[C]	1	46.0	-	7.9	-

Data are presented as mean ± SD (median) and ranges.

[A]Intravenous: Includes total nitrogen content of PN regimens, as well as additional IV glutamine supplementation;

[B]Glutamine: Includes glutamine derived from glutamine-containing PN regimens, as well as additional IV glutamine supplementation

[C]Albumin: *Albusol 20%*

Abbreviations: PN: Parenteral nutrition

Table 4-24 Breakdown of lipid delivery according to nutritional and non-nutritional sources

Variables	N-size	Cumulative grams		% of total lipid	
		Mean ± SD (median)	Range	Mean ± SD (median)	Range
CONTRIBUTION NON-NUTRITIONAL SOURCES					
% Nutrition therapy	71	-	-	98.2 ± 6.9 (100)	58.0 – 100
% Non-nutritional sources	71	-	-	1.8 ± 6.9 (0)	0 – 42.0
NUTRITION THERAPY LIPID BREAKDOWN					
Intravenous	14	239.4 ± 130.6 (210.5)	90.0 – 495.1	76.0 ± 26.2 (89.6)	36.2 - 100
Enteral	67	283.6 ± 131.3 (280.3)	14.3 – 599.3	87.8 ± 25.9 (100)	2.8 - 100
Oral	7	12.1 ± 10.0 (9.8)	0.3 – 25.0	4.1 ± 3.5 (4.1)	0.1 – 9.9
NON-NUTRITIONAL LIPID BREAKDOWN					
Propofol	7	81.7 ± 70.6 (60.0)	13.0 – 221.2	17.9 ± 14.9 (12.6)	4.6 – 42.0
Data are presented as mean ± SD (median) and ranges.					

4.7.5 Subgroup analyses

No significant correlation was found between the percentage contribution of NNES to TED and the following variables:

(1) Gender

(2) Severity of illness (APACHE II score) on admission to ICU

(3) Nutritional status (BMI) on admission to ICU

(4) Admission category

(5) Primary admission diagnosis

(6) Presence of severe sepsis or septic shock

(7) Total study hours

(8) Hours to initiation of NT

4.7.5.1 Acute kidney injury (AKI)

Patients with AKI-ND (no dialysis, n=15) had the highest percentage contribution from NNES compared to patients with AKI-D (dialysis, n=16) and normal renal function (n=40) (16.4 ± 10.0 vs 8.5 ± 5.5 vs 8.2 ± 6.0, p=0.02 respectively). The daily provision of non-nutritional calories to AKI-ND was significantly higher compared to patients with AKI-D and normal renal function (p=0.04, non-parametric Kruskal-Wallis test) (Figure 4-11).

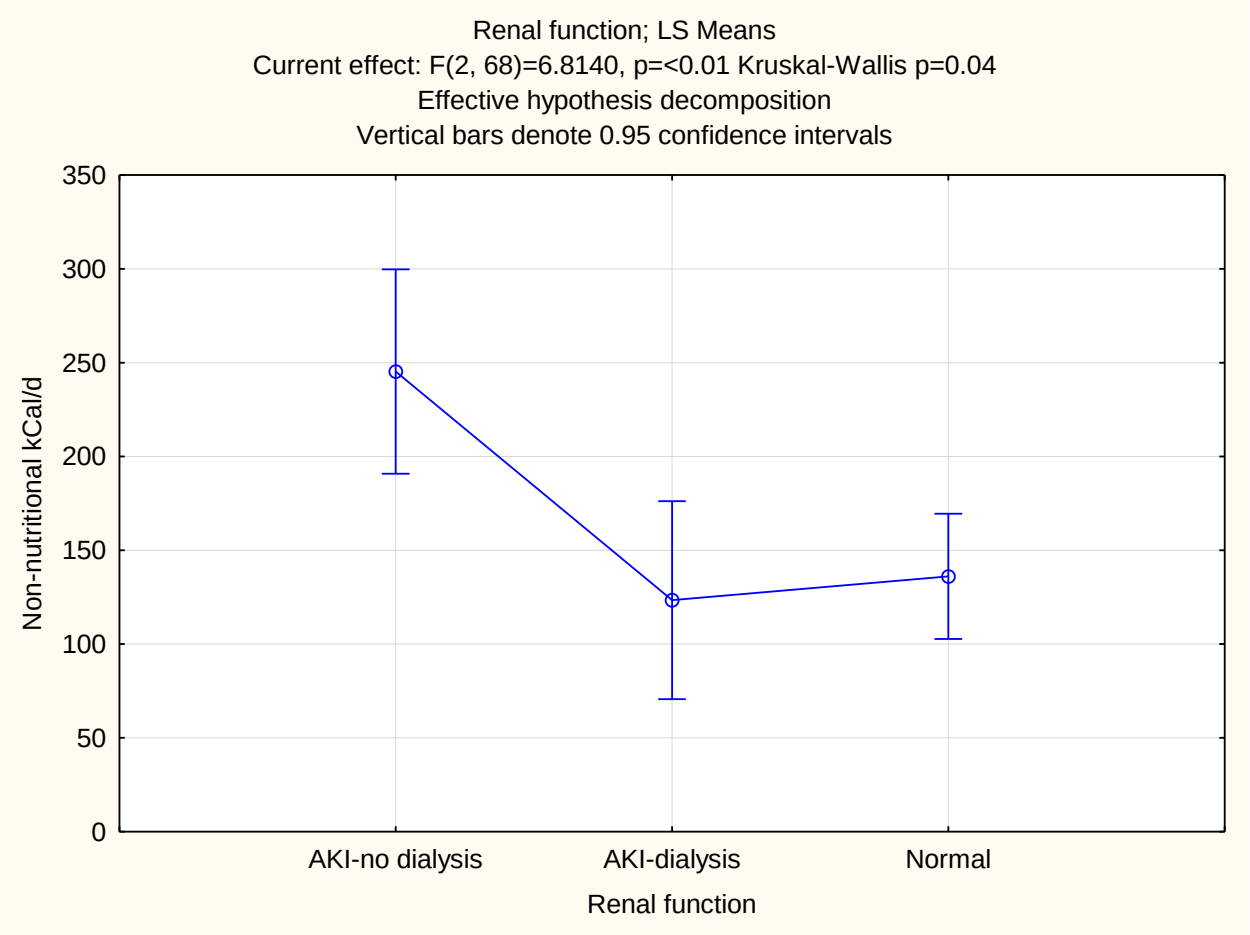

Figure 4-11 Daily non-nutritional energy provision according to renal function

The above finding can be ascribed to a significantly higher mean daily administration of glucose solutions, i.e. 5 % dextrose water, to patients with AKI-ND (n=11) compared to AKI-D (n=7) and normal renal function (n=21) (0.6 ± 0.4 vs 0.2 ± 0.1 vs 0.3 ± 0.2 L/d respectively, p=0.03). Table 4-25 shows a breakdown of the percentage contribution of different NNES to total energy and carbohydrate delivery according to the presence of AKI.

Table 4-25 Percentage contribution of NNES to TED according to renal function

	NRF	N	AKI-no dialysis	N	AKI-dialysis	N	P-value
Energy							
IV fluid therapy	6.0 ± 3.4	35	10.7 ± 7.2	15	4.5 ± 2.9	15	0.04
Crystalloids	4.8 ± 3.3	24	8.6 ± 4.5	11	3.0 ± 1.8	10	<0.01
Colloids	2.9 ± 2.7	31	5.0 ± 3.7	13	3.1 ± 2.4	12	0.17
Drug dilution	3.4 ± 2.7	12	2.1 ± 1.7	10	2.9 ± 2.0	19	0.367
Carbohydrates							
IV fluid therapy	11.7 ± 6.3	35	19.9 ± 12.1	14	8.3 ± 4.8	15	0.01
Crystalloids	9.5 ± 6.1	24	15.6 ± 8.2	11	5.7 ± 2.8	10	<0.01
Colloids	5.9 ± 5.2	31	8.8 ± 6.2	13	5.7 ± 4.3	12	0.24
Drug dilution	5.6 ± 3.6	19	6.0 ± 4.3	12	3.9 ± 2.9	10	0.38

Abbreviations: NRF: Normal renal function; AKI: Acute kidney injury; IV: Intravenous

4.7.5.2 Hypernatremia

Table 4-26 shows the spearman rank correlation analyses between “hypernatremia days” and energy delivery parameters. “Hypernatremia days” were defined as the number of days a study participant’s serum sodium concentration exceeded 149 mmol/L; i.e. cut-off point above which 5% dextrose water is used for IV drug dilution and the feeding prescription is changed to a sodium-restricted feed.

Table 4-26 Correlation analyses between hypernatremia days & energy delivery parameters

		Total cumulative delivery		% of total delivery	
Variables	**n-size**	**R**	**p-value**	**R**	**p-value**
ENERGY DELIVERY					
Total cumulative	71	0,025081	0,835526	-	-
Mean daily g/d	71	0,002027	0,986614	-	-
Mean daily g/kg/d	71	-0,057423	0,634315	-	-
Non-nutritional energy sources					
IV fluid therapy	65	0.418	0.001	0.370	0.002
Crystalloids	45	0,262358	0,081672	0.301	0.045
Glucose solutions	38	0.401	0.013	-	-
IV drug dilution	41	0.747	0.000000	0.598548	0.000036
Energy parameters					
Mean percent goal	71	-0,079364	0,510603	-	-
Cumulative energy balance	71	-0,091518	0,447823	-	-
CARBOHYDRATE DELIVERY					
Total cumulative	71	0,125830	0,295743	-	-
Mean daily g/d	71	0,154929	0,197021	-	-
Mean daily g/kg/d	71	0,107302	0,373107	-	-
Non-nutritional CHO sources					
IV fluid therapy	64	0.421011	0.000532	0.378555	0.002039
Crystalloids	45	0,258186	0,086824	0,291347	0,052164
Glucose solutions	38	0.395124	0.014082	-	-
IV drug dilution	41	0.746849	0.000000	0.638783	0.000007

Abbreviations: R: Spearman rank correlation coefficient

A significant positive correlation was found between the number of hypernatraemia days and the percentage contribution of NNES to total energy and carbohydrate delivery. This is because hypernatraemia frequently developed as a consequence of free water losses for which the administration of 5% dextrose water is clearly warranted.[57] Interestingly, there was no significant association between the number of hypernatremia days and total cumulative energy delivery, mean daily energy delivery, cumulative energy balance, mean percent goal or the percentage contribution of carbohydrates to total energy delivery. This indicates that the increase in non-nutritional calorie provision was accompanied by a simultaneous

reduction in calorie provision from NT. This could be explained by the use of sodium-restricted enteral feeding prescriptions that is often calorie-restricted.

4.8 Total energy and protein delivery in relation to estimated targets

4.8.1 Mean percent target

Overall study participants (n=71) had a mean percent target of 93.6 ± 17.7 % and 82.8 ± 19.9% (range 23.5 – 103.3) for energy and protein delivery respectively.

There was no significant correlation between energy or protein mean percent target and severity of illness (APACHE II score) on admission, total study hours or study duration post initiation of NT. There was no significant association between gender or route of feeding and the mean percent target for energy and protein. Contrary to energy delivery a significant inverse correlation was found between the protein mean percent target and BMI (n=71, R= -0.268453, p=0.023599) on admission to ICU. Hence the higher the BMI, the lower the protein mean percent target.

There was a significant negative correlation between the energy and protein mean percent target and time (hours) to initiation of NT (energy: n=71, R= -0.280370, p=0.017874; protein: n=71, R= -313428, p= 0.007778). Hence the longer the time to initiation of NT, the lower the energy and protein mean percent target. Figure 4-12 uses the mean percent target to classify patients as either energy/protein underfed (<90% of minimum target), energy/protein targets met (90% - 110% of target range) and energy/protein overfed (>110% of maximum target).

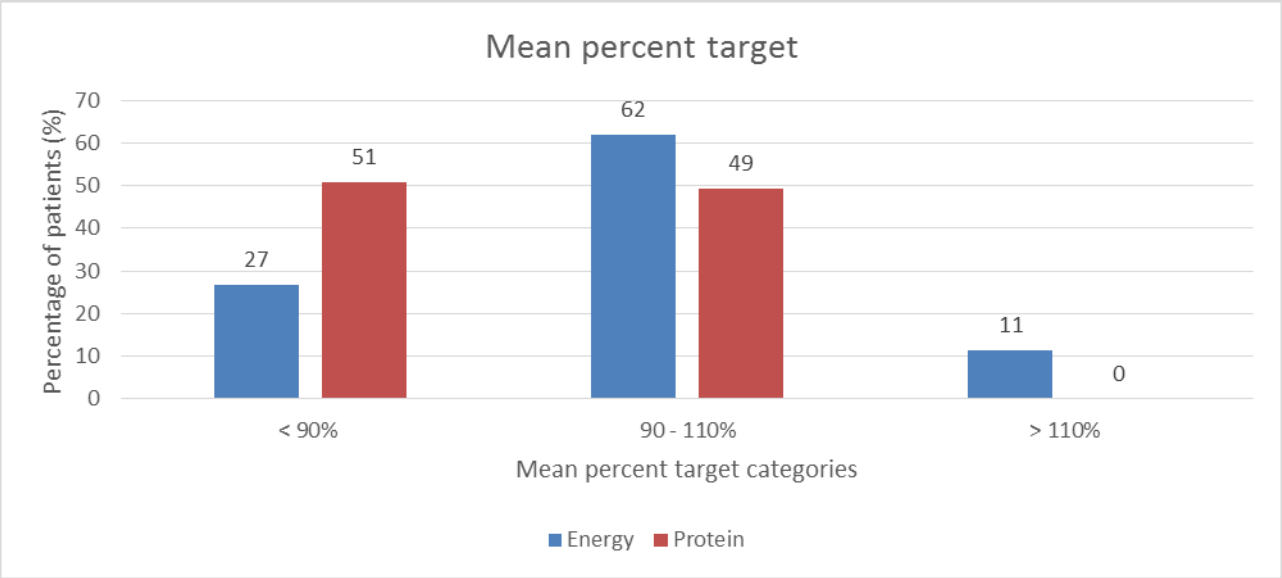

Figure 4-12 Energy and protein mean percent target

Forty-four (62%) of the seventy-one study participants achieved the energy target range, whereas only thirty-five (49%) achieved the protein target range. Only nineteen study participants (27%) were energy underfed whereas thirty-six (51%) were protein underfed. Although eight patients (11%) exceeded the maximum energy target, none exceeded the maximum protein target.

4.8.2 Cumulative balance

Overall study participants (n=71) had a mean cumulative energy and protein balance of -674.0 ± 1866.1kCal and -86.0 ± 106.9g protein (range -546.3 – 11.7) respectively.

There was no significant correlation between cumulative energy and protein balance and severity of illness (APACHE II score) on admission, total study hours or study duration post initiation of NT. There was no significant association between gender or route of NT and cumulative balance for energy and protein. Contrary to energy delivery a significant correlation was found between cumulative protein balance and BMI on admission to ICU (n=71, R=-0.286704, p=0.015348). Hence the higher the BMI, the lower the cumulative protein balance.

There was a significant negative correlation between cumulative energy and protein balance and the time (hours) to initiation of NT (energy: n=71, R= -0.283345, p=0.016647; protein: n=71, R= -0.324926, p= 0.005697). Hence the longer the time to initiation of NT, the greater the cumulative energy and protein debt.

4.8.3 Subgroup analyses

Table 4-27 shows a breakdown of the mean percent target and cumulative balance according to the primary admission diagnosis. Gastrointestinal patients, presumably mainly surgery participants, had a significantly lower mean percent target and cumulative balance for both energy and protein delivery. This can be ascribed to longer NPO periods prior to initiation of NT, as well decreased EN tolerance.

Table 4-27 Mean percent target & cumulative balance based on primary admission diagnosis

	GIT (n=10)	Sepsis (n=20)	Neuro (n=13)	Resp (n=17)	Other (n=11)	P value
MPT						
Energy	79.9 ± 24.6	93.6 ± 19.7	100.6 ± 9.6	99.2 ± 13.5	89.3 ± 13.2	0.030
Protein	68.2 ± 25.8	78.3 ± 22.0	89.1 ± 11.1	92.8 ± 15.2	81.1 ± 15.8	0.02
CB						
Energy	- 2048.0 ± 2727.6	-749.6 ± 2017.1	49.7 ± 1041.4	-61.8 ± 1355.0	-1089.1 ± 1518.7	0.03
Protein	-143.1 ± 119.6	-123.2 ± 140.5	-52.1 ± 53.0	-32.2 ± 69.5	-89.6 ± 78.0	0.023

Data are presented as mean ± SD. Statistical analyses based on One-Way Analysis of Variance F-test/Kruskal-Wallis test. *Abbreviations*: MPT: Mean percent target; CB: Cumulative balance; Neuro: Neurological; Resp: Respiratory

Table 4-28 shows a breakdown of the mean percent target and cumulative balance for energy and protein according to the presence of AKI. Patients with AKI-ND had a significantly lower energy and protein mean percent target and greater cumulative energy and protein debt.

Table 4-28 Mean percent target and cumulative balance based on renal function

	Normal (n=40)	AKI-no dialysis (n=15)	AKI-dialysis (n=16)	P value
MPT				
Energy	96.2 ± 17.9	88.2 ± 15.8	92.4 ± 18.5	0.04
Protein	89.3 ± 17.2	68.6 ± 17.2	79.6 ± 21.6	0.001
CB				
Energy	-442.8 ± 1900.4	-1122.6 ± 1500.7	-831 ± 2095.1	0.04
Protein	-49.4 ± 81.5	-144.3 ± 79.0	-122.7 ± 147.7	<0.01

Data are presented as mean ± SD. Statistical analyses based on One-Way Analysis of Variance F-test/Kruskal-Wallis test. *Abbreviations*: MPT: Mean percent target; CB: Cumulative balance; AKI: Acute kidney injury

4.8.4 Impact of NNES on mean percent target and cumulative balance

There was no significant association between daily non-nutritional energy provision (kCal/d) and energy target group; i.e. underfed vs energy targets met vs overfed (p=0.91, data not shown). However, further analysis showed a significant variation between daily crystalloid-derived non-nutritional energy provision (kCal/d) and the energy target group (p=0.04) (Figure 4-13). Participants who were overfed received a significantly higher amount of calories from crystalloids.

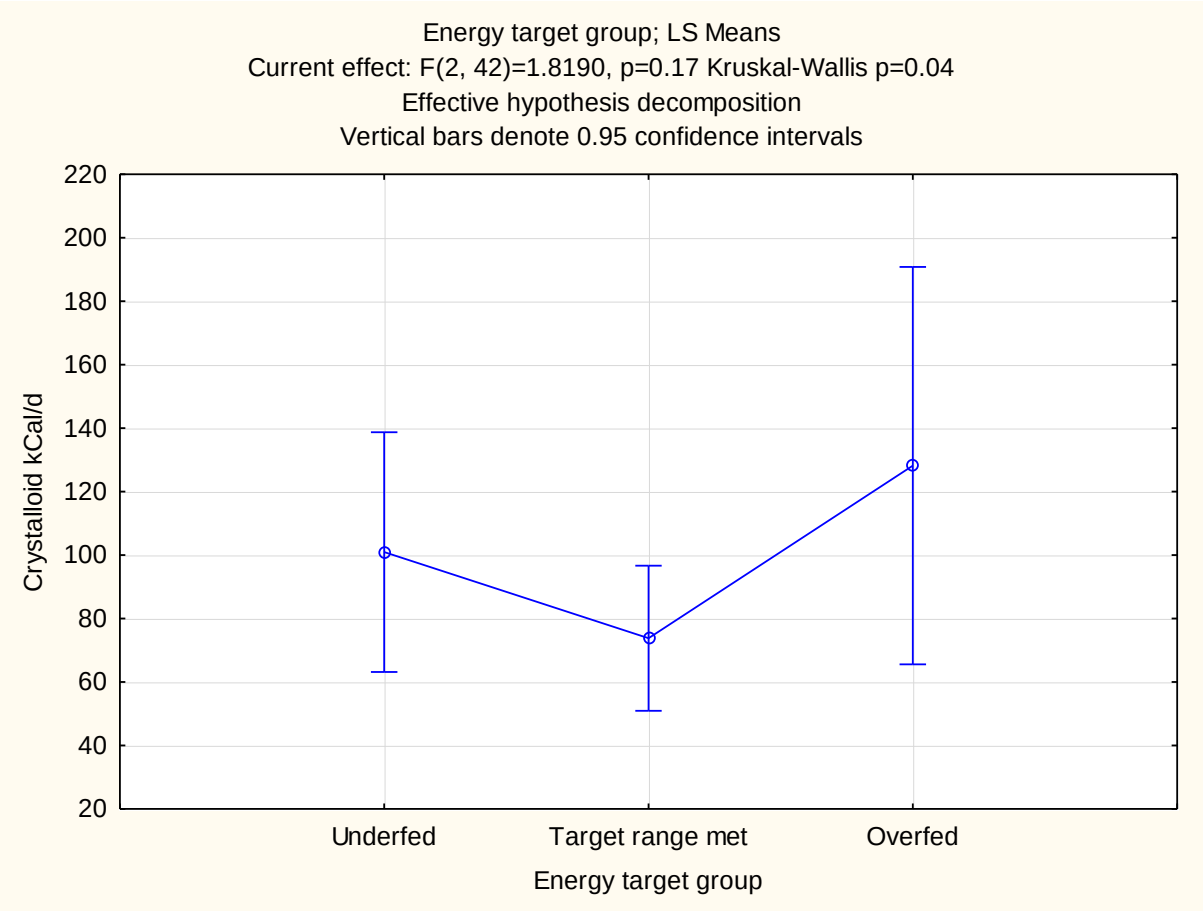

Figure 4-13 Mean daily crystalloid delivery according to energy target group

Participants who were underfed had a significantly higher percentage contribution of NNES to TED (p=0.020) (Table 4-29). The percentage contribution of NNES to TED will therefore be higher in ICUs where underfeeding is more prevalent.

Table 4-29 Percentage contribution of NNES according to energy target group

Energy target group	n-size	Mean ± SD (median)	Range	p-value*	p- variances
All groups	*71*	*10.1 ± 7.5 (8.2)*	*0 – 29.1*	-	-
Meeting energy target*	44	9.1 ± 6.5 (7.4)	0.4 – 27.7	0.149	0.088
Underfeeding*	19	13.1 ± 9.6 (12.9)	0 – 29.1	0.036	0.020
Overfeeding*	8	8.3 ± 5.3 (8.9)	0 – 15.9	0.486	0.292

*p-value: Based on T-test for independent samples (groups); Meeting energy target: Meeting 90 – 110% of the energy target range; Underfeeding: Meeting less than 90% of the minimum energy target; Overfeeding: Meeting more than 110% of the maximum energy target.

CHAPTER 5
DISCUSSION

5.1 Baseline characteristics and presence of severe sepsis, septic shock and AKI

This study retrospectively reviewed the total fluid, electrolyte, energy and macronutrient intake of 71 critically ill adult patients admitted to a medical/surgical ICU. Approximately two-thirds (68%) of the study sample were medical admissions and study participants were mostly admitted for sepsis (28%), respiratory (24%), neurological (18%) and gastrointestinal (14%) conditions. Patients in our study were younger (mean age 49) than previously published single- and multicenter observational studies in which the average age ranged between 55 and 68 years.[12,33-34,68,74,76,91-92] This may be a reflection of the lower life expectancy in developing countries, such as South Africa, compared with first-world countries where previous studies were mostly undertaken (e.g. Canada, USA, Netherlands).The average BMI on admission to ICU was 28.5 kg/m^2 and is similar to a prospective, multicentre, observational study by Heyland DK (2011) conducted in three medical/surgical ICUs. In this study, as in ours, approximately two-thirds (Heyland: 73%; this study: 68%) were medical admissions.[91]

The high prevalence of pre-obesity (28%) and obesity (32%) on admission to ICU reflects the increasing prevalence of overnutrition in the South African population. More than half of the study participants (60%) had a BMI >25 kg/m^2 and is similar to the study by Caesar et al (2011) in which 57% were either pre-obese or obese. According to McClave et al [78] based on U.S. and worldwide trends, the prevalence of obesity in the critical care setting is expected to increase over the next 10 years which is of concern since assessment of nutritional status and nutrient provision is problematic in this specific subgroup of patients.[77] Obese critically ill patients may experience greater losses of LBM with a greater risk of protein malnutrition.[28,78]

One should however bear in mind that in this study BMI was based on the anthropometrical measurements (weight and height) recorded on the study participants' ICU charts on admission to ICU. Firstly, on its own, BMI is not an accurate indicator of the presence of protein energy malnutrition (PEM), especially in obese patients who may have low muscle stores and subsequent PEM, as well as elderly patients who may suffer from age-related muscle atrophy (sarcopenia). The relationship between BMI and LBM is further hampered by systemic inflammation, sodium retention, and fluid resuscitation causing an artificial increase in body weight (and hence BMI).[93] Secondly, it is expected that patients with a

normal or high BMI on admission will develop subsequent PEM with a prolonged ICU stay, due to a number of factors, some intrinsic to the patient and some iatrogenic.[94]

A large proportion of the study sample (82%) presented with severe sepsis, either on admission (28%) or later on during the study period (54%). This is in line with the prospective observational study in a medical-surgical ICU by Allingstrup et al in whom 89%, on average, presented with severe sepsis.[92] Almost half of the study sample (44%) presented with AKI. This is slightly higher than the reported incidence of 25 – 40% reported by Fiaccadori [95], but in line with previous authors reporting an incidence of approximately 30 (33) – 60 (66%) in critical illness.[96-97] The high prevalence of AKI is concerning, since these patients have a significantly higher morbidity and mortality and managing their fluid and electrolyte status is particularly challenging.[2] In our study a significant association was found between the severity of illness (APACHE II score) on admission to ICU and the presence of AKI. This is expected since markers of AKI; i.e. raised serum levels of creatinine and potassium, form part of the physiological variables used for rating a patient's APACHE II score. According to Fiaccadori et al [95] AKI can be seen as an indicator of the severity of illness since it usually forms part of multi-organ failure secondary to severe sepsis/SIRS, with mortality rates reaching 50% of patients.

5.2 Fluid delivery

Fluids were mostly administered via the IV route (63%). The greatest contributor to total IV fluid delivery was in the form of crystalloids, colloids and blood products (52%) followed by IV drug administration (35%). In this study IV drug administration took into account the volume of all liquid drugs, as well as fluids used for reconstitution and dilution purposes. If data pertaining to drug administration were not charted (e.g. flushing of IV lines, reconstitution of powdered drugs, IV drug dilution) a standardized procedure (Addendum B) was followed to estimate the given fluid volume accurately. This standardized procedure was based on the precise administration policy as indicated on the drug's package insert or as per standard ICU protocol for the administration of drugs.

The mean daily IVFT volume of 1.1L/day reflects the use of a more restrictive fluid therapy regimen. This is in line with the recommendation by Hilton et al [35] suggesting the use of a more restrictive approach instead of the "fixed 3 L per day" prescription for maintenance fluid requirements. More recently Brettner et al [4] strongly suggested against excessive IV fluid administration due to the vast body of evidence linking it to the shedding of the endothelial glycocalyx with a subsequent increase in vascular permeability and interstitial oedema.

However, despite the relatively low daily administration of crystalloids, colloids and blood products (32% of total fluid delivery), total fluid delivery was considerably higher (3.2 L/day) due to additional IV fluid delivery; especially IV drug administration which contributed a further 21% to total fluid delivery. To our knowledge this is the first study to accurately take into account the volume of all liquid drugs, fluids used for reconstitution and dilution purposes, as well as flushing of IV lines. Our study therefore confirms the recommendation by Rassam et al [39] that the volume of multi-drug infusions, PN, EN or antibiotics requiring large volume infusions should be added to the maintenance fluid regimen such that an accurate balance is recorded. Additional fluids given to provide adequate nutrition and drugs should also be compensated for in the prescription of fluid removal in patients receiving CRRT for AKI.[10]

Balanced electrolyte solutions (e.g. Balsol/Plasmalyte B, Hartman's solution/Ringer's Lactate) were the crystalloid of choice for IVFT. Non-hypertonic LMW 130/0.4 KD HES was prescribed for the treatment of acute hypovolemia, while the use of albumin and gelatins was practically negligible (0.6%). The choice of IV fluids in this unit are in line with recent publications suggesting the use of balanced tetrastarch iso-oncotic colloids to restore cardiac output, whilst restricting the use of balanced crystalloid solutions to the replacement of extracellular losses or dehydration.[3-4,20] The concept of "demand-oriented perioperative infusion therapy" suggested by Brettner et al also supports this approach to IVFT.[4] On the other hand international regulatory bodies issued recent statements that HES IV fluids should be withdrawn from clinical use; (2) its clinical use reviewed; or (3) used with extreme caution in ICU, cardiac surgery and patients with known kidney disease or coagulopathy.[52-54] These recommendations are however based on studies that administered outdated HES in excessive amounts over prolonged periods of time [50] and in elderly, critically ill septic patients.[45-46] In our study unit the use of HES was restricted to non-hypertonic LMW 130/0.4 KD HES with a relatively low mean daily volume of 0.2 ± 0.1 litres administered to a relatively young patient group (mean age 49 years).

Surgical participants (n=23) had a significantly higher mean daily fluid delivery ($p<0.01$), with a significantly higher percentage contribution from IVFT ($p<0.01$), compared to their medical counterparts (n=48). This can be explained by a higher need for post-operative fluid replacement for the following reasons:[3-4,20]

- Higher colloid and blood product delivery to treat acute hypovolemia caused by intraoperative blood loss.

- Higher crystalloid delivery to replace ECF losses caused by preoperative fasting, especially in patients who received bowel preparation, as well as insensible losses during surgery, especially in major abdominal surgery.

Non-dialysed AKI participants (p=0.01) had a significantly higher mean daily fluid delivery, with a significantly higher percentage contribution from IVFT (p=0.003), compared to their dialysed counterparts and those with normal renal function. This can be explained on the basis of the Acute Dialysis Quality Initiative (ADQI) consensus definition of AKI, denoted by the acronym RIFLE. This acronym classifies AKI into three stages of increasing severity- risk, injury and failure- and two outcome classes- loss and end-stage renal disease. AKI in ICU is often associated with pre-renal failure secondary to hypovolemia.[98] In our study, the non-dialysed AKI patients most probably represented stage 2 (Injury) of the RIFLE acronym. During this stage IVFT forms the cornerstone of management to correct a state of volume depletion in order to avoid further exacerbation of renal injury. Renal replacement therapy (RRT) is only initiated once AKI has reached stage 3 (Failure). Therefore, in our study, study participants who received dialysis most probably represented stage 3 (failure).[98] Fluid overload in the presence of AKI is also a common indication for dialysis.[99] Dialysed patients are therefore more likely to present with some degree of fluid overload with the use of more restrictive IV fluid regimens.[99] This might further explain the lower IVFT volume in this subgroup (AKI-dialysis) compared to their non-dialysed (AKI-ND) counterparts.

5.3 Electrolyte delivery

Our study confirmed that IV electrolyte supplementation is a routine ICU practice [8] and that nearly all patients will receive some form of IV electrolyte supplementation during the first week of ICU care. Potassium salts were the most frequently prescribed IV electrolyte supplement and were administered to 91% of the study participants. This is in line with Todd et al [8] who reported hypokalemia as the most common electrolyte disturbance in hospitalized patients. Potassium supplementation for the treatment of hypokalemia was administered according to a standard ICU protocol, as previously suggested for improving overall electrolyte replacement and its effectiveness.[8]

5.4 Contribution of non-nutritional fluids to total fluid and electrolyte delivery

Sodium and chloride delivery was mostly derived from non-nutritional fluids (>80%). Non-nutritional sodium sources included sodium-containing crystalloids, hydroxyl-ethyl starches,

blood derivatives (i.e. *Hemosolvex, Polygams*), sodium bicarbonate supplementation and the administration of fleet enemas. Non-nutritional chloride sources included chloride-containing crystalloids, HES, polygam infusions and potassium chloride supplementation. Factors that could have contributed to the high contribution of non-nutritional sources versus NT to total sodium and chloride delivery include:

- In this ICU the use of PN is predominantly restricted to electrolyte-free regimens, hence not contributing to total sodium and chloride delivery.
- The routinely used IVFT products, i.e. electrolyte solutions and HES, both contain sodium and chloride.
- Almost half (45%) of the study participants who received EN presented with hypernatremia (s-Na ≥ 149) and therefore received sodium- and chloride restricted EN formulae.

The significantly lower contribution of IVFT to total chloride delivery among patients with higher APACHE II scores on admission to ICU could be due the prescription of chloride-restricted or chloride-free crystalloids to more severely ill patients due to an increased incidence of hypernatremia (5% dextrose water), AKI and metabolic acidosis (sodium bicarbonate added to 5% dextrose water).

Calcium, magnesium and phosphate delivery was determined to a large extent by the delivery of NT with 88%, 85% and 75% of total intake derived from NT respectively. This can firstly be ascribed to the fact that IVFT products are generally low in these electrolytes. Secondly, 94% of the study participants received EN, either on its own or in combination with PN or oral nutrition. EN formulae are high in calcium, magnesium and phosphate. On the other hand PN regimens provide little or no calcium, magnesium and phosphate.

Overall, NT was the largest contributor to potassium, calcium, magnesium and phosphate delivery, whereas non-nutritional fluids were the largest contributor to total fluid, sodium and chloride delivery. The frequent use of low sodium- and chloride feeding prescriptions may have contributed to this finding. Important to note is that the electrolyte content of the prescribed drugs, e.g. sodium-containing antimicrobial agents, were not taken into account and would have further contributed to total electrolyte intake.

5.5 Energy and nutrient delivery

5.5.1 Impact of NNES to total energy and macronutrient delivery:

Table 5-1 shows a summary of the NNES that were taken into account by previously published studies assessing energy intake in ICU. It includes studies published both prior to, as well as after the data collection phase of our study (2005 – 2013). This table is based on the NNES that were reported by the respective authors.

Table 5-1 NNES taken into account by previously published observational studies

	IV fluid therapy			Drug dilution	50% dextrose water	Propofol	Polygam
	Crystalloids	**HES**	**Albumin**				
Villet 2005 [33]	X	-	-	X	-	X	-
Hise 2007 [34]	X	-	-	-	-	X	-
Alberda 2009 [74]	-	-	-	-	-	X	-
Tsai 2011 [68]	X	-	-	-	-		-
Arabi et al 2011 [70]	X	-	-	-	-	X	-
Weijs 2012 [76]	X	-	-	-	-	X	-
Allingstrup 2012 [92]	-	-	X	-	-	X	-
Singer P 2012 [72]	(X) [A]	-	-	-	-	X	-
Heidegger 2013 [32]	-	-	-	X	-	X	-
This study	X	X	X	X	X	X	X

[A] Singer P 2012 (TICACOS): The authors did not specify the type of IV fluids taken into consideration; the assumption is made (based on previous studies) that at least dextrose-containing crystalloids were included in their calculation of energy intake.

These studies did not take into account all of the existing NNES. To our knowledge, this is the first study to take into account the energy content of HES, *polygam* infusions, as well as the administration of 50% dextrose water used in routine ICU practices, for example, in the management of hypoglycemia and hyperkalemia.

In this study, NNES contributed 10% to total energy delivery (mean), ranging from 0 – 29% across all study participants. The percentage contribution was greater than 10% in 39% of the study participants and was the highest among underfed patients, since they had the

lowest overall energy intake. The percentage contribution of NNES might therefore be substantially higher in ICUs where underfeeding is more prevalent compared to our study unit in whom only 27% of the study participants were energy underfed.

In this study, daily energy delivery from NNES was 156kCal/day (mean), ranging from 0 – 561 kCal across all study participants. It was previously reported that NNES contribute approximately 125 kCal/d and 250kCal/d in medical and surgical patients, respectively.[34] Villet et al [33] also reported an additional 150 – 600kCal/d delivery from glucose and sedative lipids on days without feeding. In a randomised trial by Arabi et al [70] the average daily caloric intake derived from propofol and dextrose infusions was 34kCal/day and 116kCal/d respectively. The authors did not specify the sources of dextrose energy that were evaluated. Hence it is unknown whether dextrose energy derived from IV drug dilution and 50% dextrose water were included in the calculation of total energy intake. Our study results are in agreement with Heidegger et al [32] stating that NNES contribute 100 – 400kCal per day (based on the authors' experience). In the recently published tight calorie control study (TICACOS) by Singer et al, [61] energy intake guided by repeated indirect calorimetry measurements (study group) was associated with an increased length of ventilation, length of ICU stay and risk of infection, compared to a standard 25kCal/kg feeding prescription (control group). According to Heidegger et al [32] this could have been the result of systematic overfeeding, as evidenced by a significant positive cumulative energy balance in the study group (study group: 2008 ± 2177; control group: -3.550 ± 4.591; p= 0.01). Although the investigators did not take into account non-nutritional energy delivery in their target feeding prescriptions, they included it in their calculation of energy balances.[61] This speaks to the fact that targeting full energy needs, as determined by indirect calorimetry, without taking NNES into account may lead to systematic overfeeding. It also shows that systematic overfeeding is associated with potentially detrimental outcomes that may be even worse than that of underfeeding.

Non-nutritional energy delivery was mostly derived from carbohydrate-containing IV fluids, whereas in the study by Hise et al [34] more than 50% of the non-nutritional energy was derived from propofol. In the latter study 70% of the surgical patients received propofol which is not a routinely used sedative agent in our unit and use was restricted to only 10% of the study sample who presented with status epilepticus. In this specific sub-group of patients (n=7) propofol provided an additional 139kCal/d, contributing 7% to total energy delivery and 18% to total lipid delivery. Our study therefore confirms previous studies by Hise et al [34] and

Taylor et al [86] recommending close supervision of propofol administration as an additional lipid source.

In the study by Hise et al [34] surgical patients received significantly more dextrose-containing IV fluids compared to medical patients (p=0.013) whereas in our study there was no significant difference between these groups with regard to the contribution of dextrose-containing IV fluids to total energy delivery. In the study by Hise et al differences in ICU and physician practices could have influenced the prescription of these fluids since medical and surgical patients were from different ICU's.

Interestingly, in our study the administration of crystalloids played a significant role in overfeeding. Patients who were overfed (n=8) received a significantly higher amount of calories from carbohydrate-containing crystalloids compared to those who were not overfed (n=63) (p=0.04). This confirms the need for dieticians to take into account non-nutritional energy delivery, including energy derived from crystalloids, when calculating feeding prescriptions. [29,31-32] The prescription of calorie-restricted feeds to compensate for additional NNES may however contribute to protein underfeeding due to the low protein to non-protein energy ratio of currently available EN products.[72,93] The dietician is therefore faced with a two pronged dilemma: Using a patient's total energy intake as a limiting factor may lead to protein underfeeding whereas the use of a protein target as the limiting factor may lead to overfeeding. Protein underfeeding is problematic, since more and more evidence suggests protein intake to be an important factor in outcome. [60,72,76,92-93]

In this study, the contribution of NNES to total protein delivery was negligible. However, intravenous albumin infusions are not a routine practice in this particular unit and may also significantly influence total protein intake in units where it is routinely used. The prospective observational study by Allingstrup et al [92] stated that the protein derived from albumin infusions was included in the calculation of total protein intake. However the authors did not give feedback on the actual amount of albumin that was given and its contribution to total protein intake.

This study identified four patient subgroups in which close supervision of non-nutritional energy provision might be warranted:

- Gullian-bare syndrome (GBS):

These patients often receive high-dose immunoglobulin therapy through a continuous Polygam infusion. In our study only three study participants presented with GBS and hence precluded any statistical inferences.

- AKI not receiving dialysis:

This subgroup represents the “Injury” stage of the RIFLE criteria for AKI. IVFT in the form of glucose or gluco-saline solutions are often prescribed to these patients to reverse renal ischemia and/or increase renal perfusion.[98,100] These patients also tend to have higher serum sodium levels as free water clearance is increased. This patient subgroup therefore received a significantly higher administration of glucose-containing crystalloids (p=0.03) and a higher delivery of non-nutritional calories (kCal/d) (p=0.04).

- Hypernatremia:

Free water in the form of 5% dextrose water is clearly warranted in the treatment of hypernatremia.[57] In our study the longer a patient presented with severe hypernatremia; i.e. serum sodium exceeding 149mmol/L, the greater the contribution of carbohydrate-containing IV fluids to total energy and carbohydrate delivery.

- Status epilepticus:

Propofol administration used in the treatment of status epilepticus adds to total energy and lipid intake and should therefore be closely monitored in order to prevent overfeeding.

5.5.2 Energy and protein delivery in relation to estimated requirements

Table 5-2 shows a breakdown of the mean energy and protein delivery compared to previously published studies.

Table 5-2 Mean energy and protein delivery compared to previous studies

	Energy (kCal)[A]	NPE (kCal)	Protein (g)	N_2 (g)	NPE:N
Alberda 2009 [74]	1034	846	47	7.5	112:1
Strack van Schijndel 2009 [101]	1730 (males) 1536 (females)	1429 1268	75 (males) 67 (females)	12.1 10.7	119:1 118:1
Weijs 2011 [76]	1728	1424	76	12.2	117:1
Singer 2012 [61]	2086	1782	76	12.2	147:1
Allingstrup 2012 [92]	1875	1537	84.7	13.5	114:1
Heidegger 2013 [32]	1949 [B]	1625	81 [C]	13.0	125:1
Our study	1613	1325	72	11.5	115:1

[A]Refer to table 5-1 for a breakdown of the NNES taken into account by the respective studies;
[B]Based on 28kCal/kg reported; [C]Based on 1.2g/kg reported
Abbreviations: NPE: Non-protein energy; N_2: Nitrogen; NPE:N: Non-protein energy to nitrogen ratio; BW: Body weight

Study participants had a mean daily energy intake of 25kCal/kg derived from both nutritional and non-nutritional energy sources and achieved 94% of the mean target range. More than two-thirds of the study sample (73%) received more than 90% of the estimated energy target range. Since 80% of the study participants were fed via the enteral route (including the 4% who received additional oral nutrition) and only 14% received a combination of EN and PN, shows that energy targets can be met without routine supplemental PN in a predominantly medical ICU, given the employment of a dedicated nutrition team, including a registered dietician, practicing individualized and goal-directed NT.

Factors that could have contributed to our good energy delivery results include:

(1) **Earlier initiation of NT compared to previous studies with poorer outcomes.** Early initiation of NT is seen as the first step in reducing a growing energy and protein deficit.[29]

(2) **Accurate calculation of energy delivery from NNES compared to previous studies.** Actual energy delivery in previous studies could have been underreported due to a failure to take NNES into account.[29]

(3) **Active role of dietician in writing individualized feeding prescriptions, the use of a combination of EN formulae, as well as delivering prescribed feeds to bed-side nursing staff on a daily basis.** According to Kiss et al [102] routine nutritional assessment by a dietician or designated nutrition support team leads to improved energy and protein delivery. Weijs et al [76] reports that their good energy and protein results were partly due to the use of individualized nutrition regimens with a combination of EN formulae aimed at reaching energy and protein targets. Interestingly, the energy and protein intake in the Weijs study was very similar to that of our study (Table 5-2).

(4) **Implementation of an enteral feeding protocol.** The use of enteral feeding protocols increases the overall percentage of goal calories provided.[67]

(5) **Awareness among physicians about the importance of early and optimal NT.** According to Singer and Cohen (2013), a recent Brazilian study by Gouveia Casto et al (2012) showed that providing nutrition education to intensive care physicians caused a significant increase in the early introduction of EN and the amount of energy delivered.[72]

Our study found a significant correlation between the time to initiation of NT and the mean percent target and cumulative balance for energy and protein delivery. On average, NT was initiated within fourteen hours of ICU admission and is substantially earlier than in recently published multicenter observational studies (45 hours on average).[12,91] Our study therefore confirms the importance of early initiation of NT in order to prevent a growing energy/protein debt.[29,33] However, despite the good results achieved with energy targets in our study, protein delivery was less favourable. It therefore seems that early initiation of NT with currently available EN formulae is insufficient to ensure adequate protein delivery and indicates an urgent need for alternative measures to optimise protein delivery during the first

week of ICU care, particularly since recently published observational studies have shown that achieving adequate protein delivery in ICU is paramount. Weijs et al [76] showed that meeting protein and energy targets is associated with a 50% decrease in 28-day mortality, whereas reaching only the energy targets is not associated with a similar mortality benefit. Furthermore, Allingstrup et al [92] found that provision of more protein and amino acids in critically illness was associated with a lower mortality, which was not the case for the provision of energy alone, measured resting energy expenditure or energy or nitrogen balances. However, until now the importance of protein intake has been grossly neglected with the primary focus revolving around meeting energy targets.[72,93] In reality most critically ill patients receive less than 50% of the most common protein recommendation (1.5g/kg per day) during their ICU stay and protein intake seldom exceeds 0.8 – 1.0g/kg/d.[72,93] Study participants had a mean daily protein delivery of 72g (1.1g/kg/d) and a mean percent target of 83%. Figure 5-1 shows previously published studies with the best protein delivery results; i.e. equal to or greater than 1.0 g/kg protein per day.

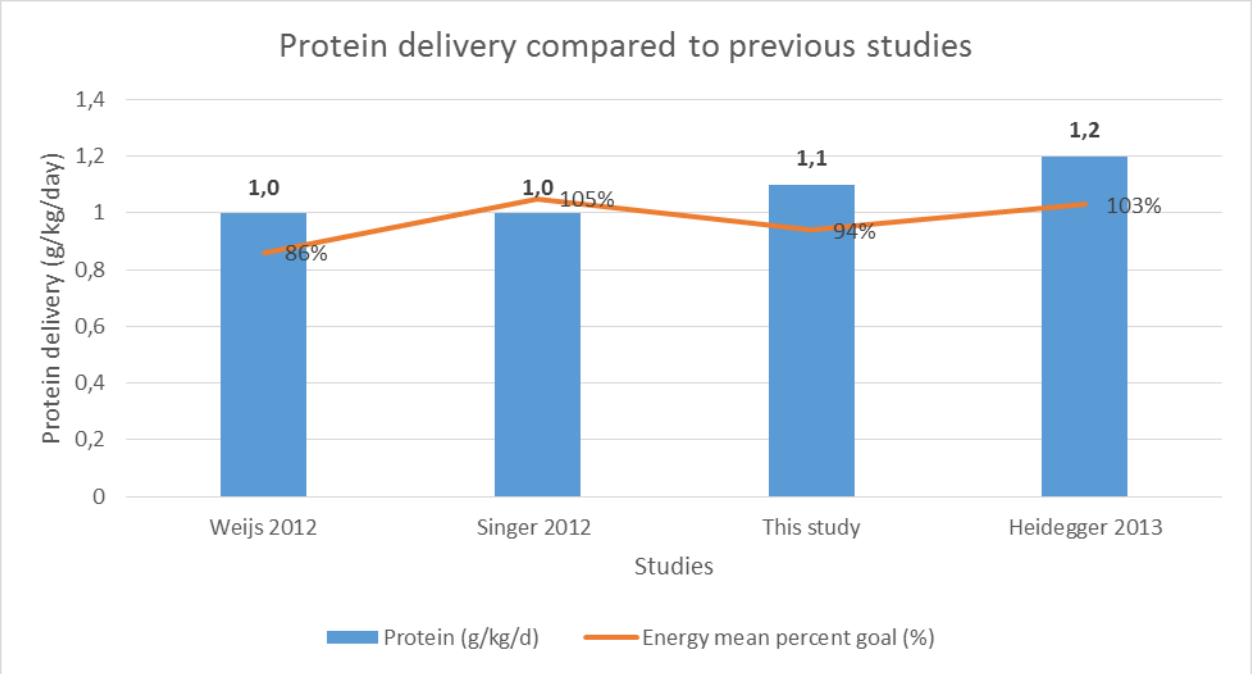

Figure 5-1 Protein delivery compared to previous studies

These studies utilised labour-intensive procedures for meeting their targeted energy and protein intake. Singer et al [61] and Heidegger et al [32] utilised supplemental PN; whereas Weijs et al [76] utilised a computer algorithm with a combination of EN formulae. Although these

studies had a favourable energy intake (>85% of target), protein delivery was less favourable. This confirms that current EN and PN products fail to provide sufficient protein such that the most commonly recommended target of 1.5g/kg/day cannot be achieved. Even labour-intensive procedures as described above fall short of the optimum time frame and rate of protein provision, which could well be 2g/kg/d or more for a large proportion of critically ill patients.[93] According to a recent systematic review by Hoffer and Bistrian [103] most critically ill patients could actually require more than 1.5g protein/kg and they strongly suggest that 2.0 – 2.5g protein/kg is safe and could be the optimum.

In this study only 49% of the study participants achieved an adequate protein intake (i.e. > 90% of minimum protein target). Figure 5-2 shows the percentage of patients in each energy target category who achieved at least 90% of the minimum protein target.

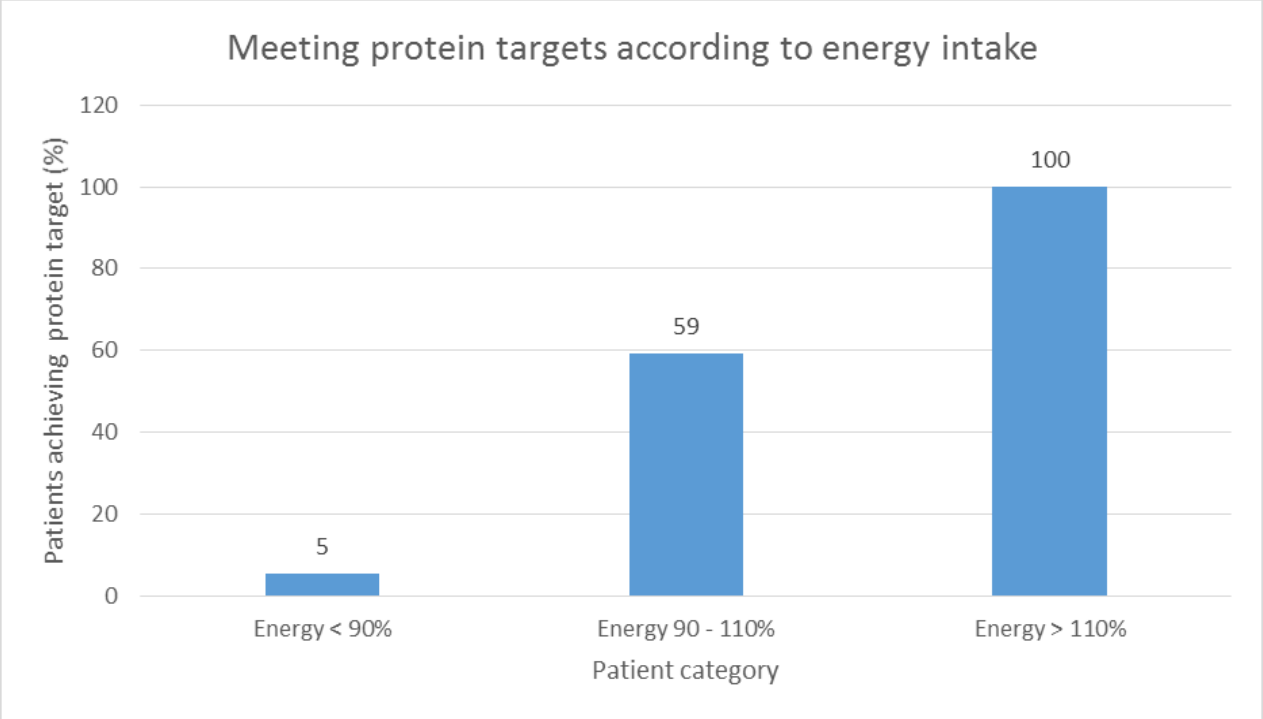

Figure 5-2 Percentage of patients receiving ≥90% of minimum protein target according to energy target group

Only 5% of those that were “energy underfed” and 59% of those that met energy targets achieved an adequate protein intake. However, all the overfed patients had an adequate protein delivery. Overfed patients are therefore most likely to have their protein targets met. This once again indicates the necessity for new EN formulations with a higher protein and

lower non-protein energy content, especially in the light of NNES primarily contributing to energy intake in the form of carbohydrates. Hoffer and Bistrian [93] agree that conventional EN generally fails to exceed 50% of a patient's protein target and that achieving adequate protein delivery will simultaneously result in an excess delivery of non-protein energy, the toxic effects of which are well recognized in critical illness. Hoffer and Bistrian further recommend the use of routine supplemental PN as a means of bridging this protein shortfall.[93] This study suggests that the routine use of lower-calorie, high-protein EN products during the first week of ICU care may offer a more cost-effective and safe way of optimising protein delivery in a predominantly medical ICU.

CHAPTER 6
CONCLUSION AND RECOMMENDATIONS

6.1 Strengths and limitations

This is the first study in South Africa to determine the contribution that IV fluid and electrolyte administration make to total fluid, electrolyte, energy and macronutrient intake in critically ill patients. Furthermore, to our knowledge, this is the first study that takes into account:

- The energy content of HES, immunoglobulin therapy (*polygam*) and the administration of 50% dextrose water in calculating total energy intake.
- The contribution of IV line flushes, the volume of liquid drugs, as well as fluids used for reconstitution and dilution purposes, in calculating total fluid intake.

Study participants' total energy and protein intake were compared to estimated energy and protein requirements and standardized according to evidence-based recommendations made by international organizations.

There are some limitations in the current study. Given the nature of the design of this study, data was obtained through a retrospective review of study participants' ICU charts. Data on fluid, electrolyte and nutrient intake was hence fully reliant on the accuracy of charted data. During our pilot study it was noted that certain required data was not routinely or accurately charted by nursing staff; i.e. flushing of IV lines, drug dilution (diluent agent and volume), and specification of the EN formula or PN regimen. To ensure data accuracy and validity the principal investigator trained all nursing staff prior to data collection with regard to accurate charting of all relevant data. An attendance register was completed (available on request) and signed by all nursing staff who received training. An information sheet was also handed out during the training session (Appendix D). The principal investigator trained the clinical facilitator of the unit to reinforce training on a regular basis to all nursing staff and to train all new staff introduced to the unit with regard to accurate recording on ICU charts.

The assumption was made that the delivery of NT was accurately charted. However, the true accuracy in the charting of short feeding interruptions (e.g. the time delay between an EN bag running empty and the bedside nurse changing the bag, measuring of residual volumes, administration of medications via the enteral feeding tube, and short procedures requiring the patient to be supine or flat, e.g. skin care, bathing the patient) is unknown.

Given the nature of the study design, no statistical inferences can be drawn on the relation between fluid or nutrient delivery and patient outcomes. Although our study identified higher

fluid delivery among certain patient subgroups, e.g. surgical and AKI patients (no dialysis), cumulative fluid balance was not determined and might be of greater value in terms of patient outcomes. Lastly, groups that were compared in the sub-group analyses (e.g. surgical vs medical) were not always equal in sample size, thereby reducing the strength of statistical inferences.

6.2 Recommendations

Post-hoc analysis determining fluid balance and its relation to patient outcomes in surgical and AKI patients is recommended. Post-hoc investigation of the relationship between energy/protein mean percent goals and patient outcomes, e.g. ventilator-free days, infection rates, ICU mortality, hospital mortality and six-month mortality should also be considered.

Similar studies with a prospective observational design and with equal numbers of subgroups to be compared (e.g. surgical vs medical patients) are recommended. Even more so, adequately powered randomized clinical trials to establish cause-effect relationships between fluid-, energy- and protein balance and patient outcomes, with total fluid and energy delivery calculated in a similar fashion to our study, is highly recommended.

Lastly, adequately powered, randomized clinical trials assessing the impact of low-calorie, high protein EN formulae on total energy and protein delivery, whilst taking nutritional and non-nutritional energy sources into account, are recommended. This is especially warranted among the “at risk” patient groups identified in our study, namely gastrointestinal, obese and non-dialysed AKI patients.

6.3 Conclusion

Our study revealed that even in the presence of a restrictive IV fluid therapy regimen, total fluid delivery is considerably higher due to additional IV fluid delivery; especially from IV drug administration. The crystalloid and colloid of choice for IV fluid therapy were balanced electrolyte solutions and hypertonic LMW 130/0.4 KD hydroxyethyl starches respectively. Potassium-salts were the most frequently prescribed IV electrolyte supplement.

In this study NNES contributed 10% to total energy delivery, but the percentage contribution might be substantially higher in other ICUs where underfeeding is more prevalent. Non-nutritional energy provision was mostly derived from carbohydrate-containing IV fluids.

Four patient subgroups were identified in whom close supervision of non-nutritional energy provision might be warranted, namely (1) gullian-bare syndrome receiving polygam, (2) status epilepticus receiving propofol, (3) non-dialysed AKI receiving high volumes of IV fluid therapy in the form of dextrose-containing crystalloids, and (4) hypernatraemic patients receiving a free water infusion in the form of 5% dextrose water.

Our study showed that energy targets can be met without routine supplemental PN in a predominantly medical ICU, given the employment of a dedicated nutrition team practicing individualized and goal-directed NT. However, it seems that early initiation of NT with currently available energy-rich EN formulae is not sufficient to ensure adequate protein delivery. The dietician is therefore faced with a dilemma: Using a patient's protein target as the limiting factor when prescribing conventional EN products may lead to overfeeding on calories which will then be further worsened by additional energy delivery from NNES. Conversely, using the energy target as the limiting factor to avoid overfeeding may lead to protein underfeeding. Both overfeeding and protein underfeeding have been associated with unfavourable patient outcomes and should be avoided.

In conclusion, although targeting of full energy and protein requirements are associated with positive outcomes in ICU, [32,61,68,74-76,91-92] it is essential to include NNES in the calculation of feeding prescriptions to avoid the harmful effects of overfeeding. Furthermore, this study stresses the need for new EN formulae with a more favourable nitrogen to non-protein energy ratio, especially in the light of the fact that NNES contribute mainly to carbohydrate intake. The routine use of such feeds may offer a more cost-effective and safer solution to the optimisation of protein delivery compared to routine supplementation of inadequate EN with PN.

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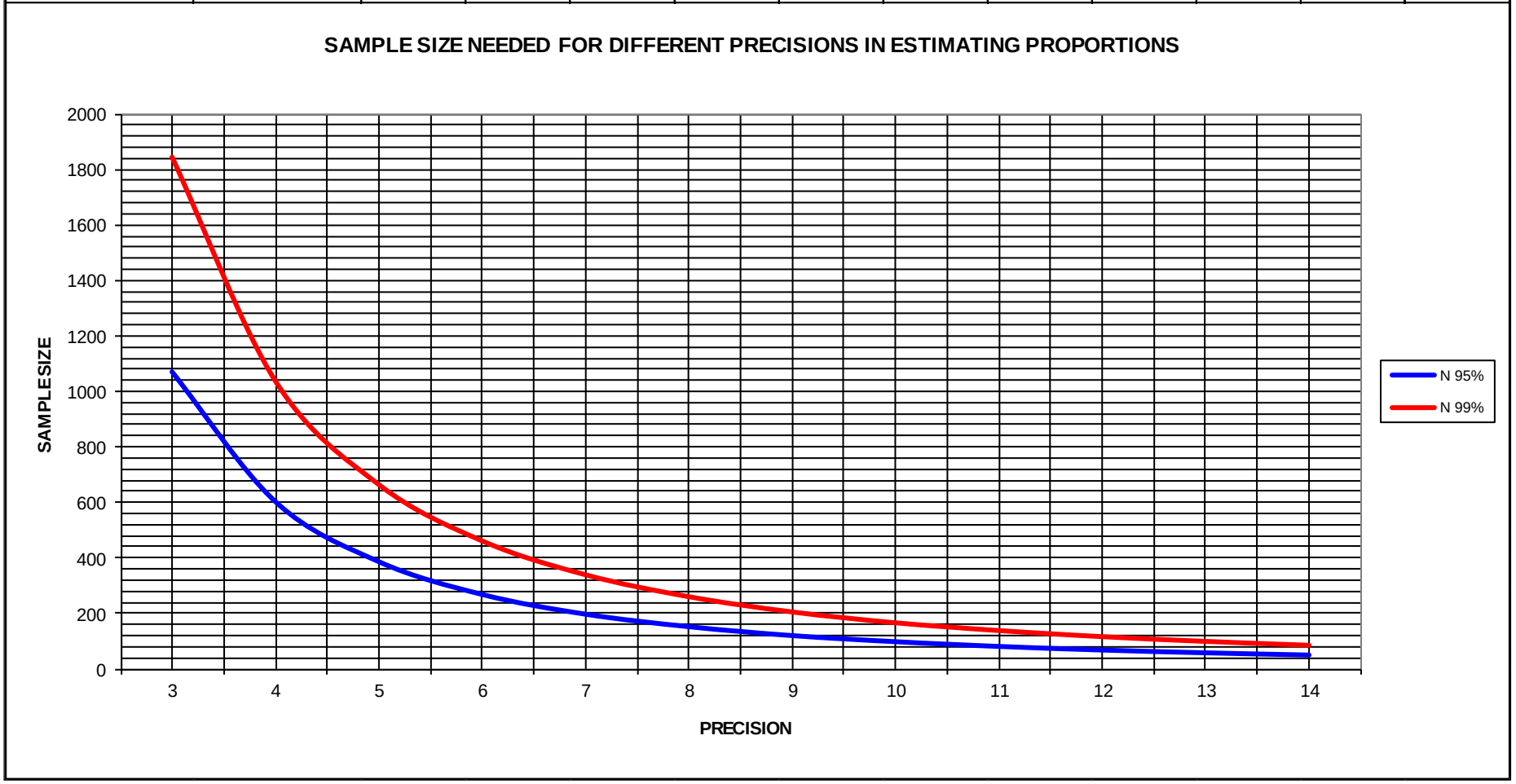
APPENDICES

APPENDIX A

SAMPLE SIZE CALCULATION

CHOOSE CONFIDENCE LEVEL		95	99									
	Alpha	5,00%	1,00%									
	Z =	1,959964	2,575829									
p	0,5	0,5	0,5	0,5	0,5	0,5	0,5	0,5	0,5	0,5	0,5	0,5
Precision	3	4	5	6	7	8	9	10	11	12	13	14
N 95%	1068	601	385	267	196	151	119	97	80	67	57	49
N 99%	1844	1037	664	461	339	260	205	166	138	116	99	85



APPENDIX B

STANDARDISED DATA COLLECTION PROTOCOL

576 GENERAL ICU (CMJAH)

CLINICAL NUTRITION RESEARCH

STANDARDISED DATA COLLECTION PROTOCOL

1. General information:

Research project title:	The Impact of Intravenous Fluid and Electrolyte Administration on Total Fluid, Electrolyte and Energy intake in Critically Ill Adult Patients.
Researcher:	Lizl Veldsman
Study leaders:	Prof GA Richards Prof R Blaauw
Contact details	Lizl Veldsman c: +2782 414 5084 w: (011) 488 4348 lizlveld@gmail.com

2. Screening

1. You will consecutively enrol patients in the study. Beginning on the first day of data collection, record all patients discharged from ICU or who demised on or after that day in the screening log (Appendix I).
2. Screening log columns represent eligibility criteria for purposes of data collection. Place a ✓ in each column where a patient meets the eligibility criteria, or an × if the patient does not meet that criteria. A research number should be allocated to each eligible patient and recorded on the screening log. Research numbers should be allocated consecutively from R1 to R70 as patients are entered into the study. Collect data on all patients who meet all eligibility criteria. If charts are missing and you are unable to collect all of the required data for a patient, please exclude this patient and include the next eligible patient. Screening should be continued until a minimum of 70 consecutive eligible patients have been reached.

   Note: Consecutive means the very next patient that meets the criteria, instead of picking and choosing patients.
3. If a patient you collected data on is later readmitted to the ICU, do not include the patient a 2nd time.
4. Use additional pages of the screening log as necessary.
5. Record each patient's hospital number on the screening log.
6. Each eligible patient's research number (e.g. R4) will be recorded on the screening log.
7. Please keep the screening log to help track down which patient corresponds to which research number in case there are data queries at a later date.

Enrol all patients meeting the following eligibility criteria:

Inclusion	Exclusion
- Adults (≥ 18 years of age) - Must have been admitted to the general ICU (576) of CMJAH. - APACHE II score ≥10 on admission to ICU. - Must have received nutrition therapy (i.e. enteral nutrition and/or parenteral nutrition) for at least 72 hours. - Must have had an ICU length of stay of at least 72 hours.	- Skeletal abnormalities, contractures and spinal cord injuries (quadriplegia and paraplegia). - Nutrition therapy discontinued within 72 hours after ICU admission. - Discharged from ICU or death within 72 hours after ICU admission.

3. Case Report Forms

1. A case report form (CRF) (Appendix II) must be completed for each study participant.
2. All data requested in the CRF is to be taken retrospectively from the original source documents, i.e. the patient's ICU chart/s or hospital file.
3. Collect data retrospectively from the day of ICU admission until discharge from ICU, discontinuation of nutrition therapy or death, whichever occurred first. If a patient remained in ICU for more than 7 days data should only be collected until day 7 in ICU.
4. Please ensure that the CRFs of each patient are complete.
5. All data fields should be completed
    - Please indicate if any given data is not charted on the patient's records.
    - **Asteriks (*) denote required fields.** If required data is not charted on the patient's records, exclude this patient and include the next eligible patient.
6. All dates must be recorded in the format YYYY-MM-DD.
7. All times must be recorded using the 24 hour (military) clock (HH:MM). Midnight will be 00:00 hr.
8. Anywhere in the CRF that "Other, specify" is indicated and/or has been selected, there must be an entry on the line provided further describing what "other" means.
9. Day 1 is the date of admission to ICU.
10. **Study days are defined according to ICU chart days (i.e. 07:00-06:59 hrs).** Study days therefore begin and end at 07:00am. This will ease data collection.
    - Day 1 might not be a full 24 hour period.
    - The last day in the ICU might not be a full 24 hour period.

a. Patient Information

Sex*	Place a ✓ in the appropriate box (male or female)
Age*	Record patient's age (year and months)
ICU Admission Date/Time*	Enter the date and time the patient was admitted to 576 ICU. If the patient has been admitted to the ICU multiple times, use the **most recent** admission. If a patient is transferred from another ICU enter the date of admission to **576 ICU**.
Type of admission*	Place a ✓ in only one of the following categories: **Medical:** defined as a patient admitted to the ICU for treatment without any surgical intervention (includes patients admitted from a cardiology/ radiology unit) **Surgical:** defined as (1) a patient admitted to the ICU from the operating room directly or a recovery unit following a planned surgical procedure or (2) a patient admitted to the ICU from the operating room or a recovery unit following an unplanned surgical procedure. *Note: If a surgical patient develops a medical complication and is transferred to the ICU from the ward, this would be a "medical" admission type.*
Primary ICU diagnosis*	Identify and write down the most pertinent diagnosis that resulted in the patient's admission to ICU. Only one diagnosis can be chosen. Remember, symptoms are not an admission diagnosis (e.g. respiratory distress, hypotension, etc.) *Example: A patient was admitted to hospital for an elective cholecystectomy. Post-operatively the patient developed septic shock on the ward and was subsequently admitted to the ICU. The patient would be classified as medical admission type, and septic shock as the primary ICU diagnosis.*
APACHE II score*	The APACHE II score must be calculated using Appendix III. *Note: For each APACHE variable, use the single worst value out of all values from the first 24 hours after ICU admission. If variables are not available from the first 24 hours, go outside the 24 hour window and use data closest to ICU admission.*
Renal function*	Review the patient's ICU charts for the presence of AKI. The presence of AKI should be based on the charted diagnoses by the attending physician. If a patient presented with AKI, please indicate whether the patient received renal replacement therapy.
Presence of sepsis*	Review the patient's ICU charts for the presence of sepsis. The presence of severe sepsis/ SIRS or septic shock should be based on the charted diagnoses and/or according to the presence of sepsis criteria as indicated in the table below.

Sepsis diagnostic criteria	
SIRS	Presence of two or more of the following features: Temperature < 36˚C or > 38˚C; (2) Tachycardia > 90 beats per minute; (3) Respiratory rate > 20 breaths per minute or P_aCO_2 < 32 mmHg; (4) WCC > 12 X 10^9/L or < 4 X 10^9/L
Sepsis	SIRS occurring in the presence of an infection
Severe sepsis	Sepsis with evidence of one or more organ dysfunctions, such as: Acute kidney injury (oligouria), thrombocytopenia, secondary acute respiratory distress syndrome (ARDS), hypotension (requiring inotropes), lactic acidosis
Septic shock	Severe sepsis with hypotension (systolic BP* < 90mmHg) despite adequate fluid resuscitation

Critical illness classification*	Based on the primary ICU diagnosis, choose the most pertinent critical illness classification (subdivided under medical or surgical) for each patient.

b. Medical follow-up:

Review study participants' ICU charts and chart the following: - Medication/s - Tests/procedures - Laboratory blood values - Arterial blood gas values - Fluid balance - Gastric aspirates - Vomiting - Stools - Clinical presentation

c. Baseline nutritional assessment

Height*	Record the patient's height charted on his/her ICU chart.
Weight*	Record the patient's weight charted on his/her ICU chart. When applicable also record the adjustment of body weight for oedema or amputations (if charted).
Body mass index (BMI)	Calculate and indicate the patient's BMI according to the charted weight and height.
Nutritional status	Indicate the patient's nutritional status according to the BMI classification system.
Calculation of ideal body weight	Ideal body weight must be calculated for all patients according to the following sex-specific guideline: ***Males:*** Height^2 (m) X 20 – 25 ***Females:*** Height^2 (m) X 19 – 24 *Note: Use the height and weight recorded on the patient's ICU chart/s.* *The "ideal body weight" does not necessarily refer to the weight used in the calculation of energy and protein targets.*

d. Daily Feeding Prescription

Daily feeding prescriptions are routinely calculated and charted for all ICU patients (charted daily on ICU charts). Review each study participant's daily feeding prescription from the day of ICU admission until ICU discharge, discontinuation of nutrition therapy or death, whichever occurred first. If no RD feeding prescription is charted for a given patient, the patient's attending physician will write a feeding prescription (e.g. over weekends). Use the patient's daily feeding prescriptions (as charted on his/her ICU charts) to record the following information. Please indicate on the CRF if any particular information was not charted on the patient's records. Remember **Asteriks (*) denote required fields.** If required data is not charted on the patient's records, exclude this patient and include the next eligible patient.

Person responsible for writing daily feeding prescription*	Indicate the person/s who calculated/wrote the patient's daily feeding prescription/s; e.g. registered dietician, attending registrar, consultant or chief physician of the ICU.
Weight used in calculation of feeding prescription	Indicate the weight used in the calculation of the feeding prescription.
Prescribed route of nutrition therapy at initial assessment*	Indicate the route of nutrition therapy **prescribed** at initial assessment.
Nutrition therapy Initiation Date/Time*	Enter the date/time EN and/or PN was initiated in the ICU, or indicate "EN and/or PN initiated prior to ICU admission". Specify the initial route of nutrition therapy; i.e. EN and/or PN.
Feeding prescription*	Indicate the charted feeding prescription/s for each day (Name of EN formula/PN regimen and goal rate). If more than one feeding prescription was charted on a particular day, chart all prescriptions for that given day.
Calculation of nutritional targets	Indicate the method/formula used to calculate nutritional requirements.
Prescribed energy and protein intake	Indicate the charted daily energy and protein target. If no energy and/or protein target is charted, refer to Section E: Standardization of energy/protein targets.

e. Standardization of energy and protein targets

Use the criteria below to retrospectively standardise each patient's energy and protein targets for each day.

Standardized procedure for estimating daily energy targets	
Pathologies	**Energy requirement** [A] **(kCal/kg/d actual BW)**
Acute and initial phase whatever the underlying disease	
With severe undernutrition	25 – 30
Without undernutrition	20 – 25 (female) 25 – 30 (male)
With obesity	20 – 25[B]
With overweight	20 – 25[C]
Except for	
Burns	40
Recovery or post-acute phase whatever the underlying disease	
With severe undernutrition	30 – 35
Without undernutrition	25 - 30
With obesity	20 – 25
With overweight	20 – 25
Except for	
Burns	40 - 45
Severe sepsis/polytrauma	30 – 35
Necrotizing pancreatitis	35 – 40
Open abdomen	30 – 35
Guillian bare syndrome	30 – 35
Toxic epidermal necrosis	35 - 40
Liver failure (hepatic encephalopathy)	30 - 35
Acute renal failure	
-Conservative management	25 – 30
-Daily dialysis	30 – 35
Other factors taken into account: glucose control, presence of pyrexia, hypercapnia	

Standardized procedure for estimating daily protein targets	
Pathologies	**Protein requirement (g/kg/d actual BW)***
General ICU patient	1.2 – 1.5
Except for:	
Parenteral nutrition	1.3 – 1.5
Liver failure with hepatic encephalopathy	0.8 – 1.2
Burns	2 – 2.5
Open abdomen	1.5 – 2
Toxic epidermal necrosis	1.5 – 2
Guillian-bare syndrome	1.5
Acute kidney injury	
Conservative management	1.2
Daily dialysis/SLED	1.5 – 1.7
CVVHD	1.5 – 2
* Use ideal body weight if overweight and adjusted ideal body weight if obese. *Abbreviations:* BW: Body weight; SLED: Sustained low-efficiency dialysis; CVVHD: Continuous venovenous Hemofiltration	

Weight used for calculations	
Nutritional status	Weight used for calculations
With undernutrition	Lower range of ideal BW[A]
With severe undernutrition	Median of actual BW and lower range of ideal BW[B]
Without undernutrition	Actual BW
With overweight	Ideal BW[C]
With obese	Adjusted ideal BW[D]
[A] Lower range of ideal BW: Body mass index of 18.5 kg/m^2	
[B] Median of actual BW and lower range of ideal BW: {(Actual BW – Ideal BW) X 0.5} + actual BW	
[C] Ideal BW: Males: Height^2 (m) X 20 – 25; Females: Height^2 (m) X 19 – 24	
[D] Adjusted ideal BW (25% correction factor): {(Actual BW – Ideal BW) X 0.25} + Ideal BW	
Abbreviations: BW: Body weight	

f. Retrospective Progress Report

Review the patient's ICU charts and write down short and concise daily progress reports.

4. Daily Fluid and Nutritional Data

Use Appendix IV (*Daily Fluid and Nutritional Flow Chart*) to retrospectively record the daily fluid and nutritional intake of each study participant, from ICU admission until discharge, discontinuation of nutrition therapy or death, whichever occurred first. Retrospective review of ICU charts should be done on consecutive days following ICU admission, even if the patient did not receive nutrition (e.g. NPO for surgery). If a patient remained in ICU for more than 7 days data should only be collected until day 7 in ICU. Use additional pages of the flow chart as necessary.

Study day 1 is from ICU admission until 07:00am the next morning. This might be less than 24 hours. Day 2 and subsequent days are labelled according to ICU chart days (i.e. 07:00am to 06:59am). This will ease data collection.

Example: A patient was admitted on March 2nd at 15:33. Day 1 begins at 15:33 and ends March 3rd at 06:59am (Day 1 is only 15hrs, 26 min long). Day 2 begins at 07:00 am, March 3rd, and ends at 06:59am on March 4th.

Note: The patient should have remained in ICU for at least 72 hours to be included in the study.

It is crucial to **record all fluids taken in via the intravenous, enteral and/or oral route**. Space is provided on the patient's fluid and nutritional flow chart to indicate the type and volume of each fluid taken in.

If the following data is not accurately charted, please follow the standardised procedure (Appendix V) to accurately estimate the type and volume of fluid administered:

- Intravenous line flushing
- Reconstitution of powdered drugs
- Intravenous drug dilution
- Administration of drugs via an enteric tube
- Swallowing of tablets

Please take note of the following:

- Intravenous line flushing:

Add an additional 72ml (3ml/hr) of normal saline to compensate for the routine automatic heparin-saline flushing of IV lines (driven by an infusible pressure bag).

- Drugs administered subcutaneously or intramuscularly:

Ignore the volume of drugs administered subcutaneously (e.g. Clexane, Recormin) or intramuscularly (e.g. Tetanis immunoglobulin/anti-tetanis toxoid; i.e. ATT) since this is regarded negligible and will not be taken into account during the calculation of total fluid intake.

Appendix I:

Screening Log

(Part of standardised data collection protocol)

SCREENING LOG

ICU 576

Please use additional copies of this page as necessary.

Screening number	Date of screening	Date of discharge/demise (specify)	Date of admission	Patient initials for all patients discharged from ICU or who demised on/after first day of data collection	Patient hospital number (GT/GP no)	Patient is ≥ 18 years old	APACHE score ≥10 on admission to ICU	Patient does not have any skeletal abnormalities, contractures and spinal cord injuries	Patient remained in ICU for ≥ 72 hours	Patient received EN and/or PN for at least 72 hours.	Patient eligible?	Research number
e.g.	*16/3*	*16/3*	*8/3*	*L Struwig*	*GT0071685*	✓	✓	✓	✓	✓	*Y*	*R1*
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
13												
14												
15												
16												
17												
18												
TOTAL ELIGIBLE: _____												

Appendix II:

Case Report Form

(Part of standardised data collection protocol)

Case Report Form Patient Hospital No:_____ Research number: _____

A. PATIENT INFORMATION

Sex*: ☐ Male ☐ Female **Age*** (year & months): _____

ICU Admission Date*: (YYYY-MM-DD):_____ Time: (HH:MM, 24h): _____

Type of admission: ☐ Medical ☐ Surgical

Primary ICU diagnosis*:

_____

_____

_____

_____

Other comorbidities or medical/nutritional problems:

_____

_____

_____

Medical history:

_____

_____

_____

_____

APACHE II SCORE:* _____

RENAL FUNCTION*: ☐ Normal renal function ☐ AKI, no dialysis ☐ AKI, dialysis

SEPSIS*: ☐ No sepsis ☐ Sepsis/SIRS ☐ Severe sepsis/SIRS ☐ Septic shock

Critical illness classification (based on primary ICU diagnosis)**:**

Medical:

☐ Cardiovascular/vascular ☐ Respiratory ☐ Gastrointestinal ☐ Neurologic

☐ Sepsis ☐ Trauma ☐ Metabolic ☐ Hematologic

☐ Other medical disease, specify_____

Surgical:

☐ Cardiovascular/vascular ☐ Respiratory ☐ Gastrointestinal ☐ Neurologic

☐ Trauma ☐ Renal ☐ Gynaecologic ☐ Orthopaedic

☐ Other surgical condition, specify_____

B. MEDICAL FOLLOW-UP

Medication

Medication	Dose	Date						

Tests/procedures

Date	Test/ Procedure	Results

Laboratory blood values

Parameter	Normal range	Date						
WCC	4.0 –10X10^9/L							
Hb	12.0 – 15.0g/dL							
Plt	178-40X10^9/L							
CRP	<10							
PCT	<0.5							
Na	135- 145							
K	3.3 – 5.3							
Cl	99 – 113							
Co2	18 – 29							
Urea	2.6 – 7.0							
Creat	60 – 100							
Ca	2.05 – 2.56							
Mg	0.65 – 1.1							
P	0.8 – 1.4							
Glucose	3 – 10mmol/L							
Other								

Arterial blood gas

pH	7.35 – 7.45							
pCO_2	35-45 mm Hg							
pO_2	80-100 mmHg							
HCO_3	21-28 mEq/L							
BE	-4 - +2							
O_2 saturation	95% - 100%							

Other parameters

Fluid balance	Intake*								
	Output*								
	Balance*								
Gastric aspirates		<200mL							
Stools		<400mL							
Urine output									
Vomiting									

Clinical presentation

C. BASELINE NUTRITIONAL ASSESSMENT

Date recorded on ICU chart:_____ (Day of ICU stay: ____)

Height (metres):*_____ **Weight** (kg):*_____ ☐ Actual ☐ Estimated

Weight adjusted for oedema?* ☐ Yes ☐ No ☐ Not charted

If yes, indicate degree of oedema: ☐ Mild ☐ Moderate ☐ Severe ☐ Not charted

If yes, show calculations (if charted):

_____

Dry weight: _____kg ☐ Not charted

Weight adjusted for amputations?* ☐ Yes ☐ No ☐ Not charted

If yes, indicate body parts amputated: _____ ☐ Not charted

If yes, show calculations (if charted):

_____

Adjusted weight: _____kg ☐ Not charted

Body mass index:*_____kg/m^2 ☐ Actual ☐ Estimated

Nutritional status* (tick the appropriate block)**:**

	Undernourished	*Grade I*	17 ≤ BMI < 18.5
		Grade II	16 ≤ BMI < 17
		Grade III	BMI < 16
	Normal		18.5 ≤ BMI < 25
	Overweight		25 ≤ BMI < 30
	Obese	*Class I*	30 ≤ BMI < 35
		Class II	35 ≤ BMI < 40
		Class III (Morbid obesity)	BMI ≥ 40

Calculation of ideal body weight:
Males: Height^2 (m) X 20 – 25
Show calculations:_____

Females: Height^2 (m) X 19 - 24
Show calculations:_____

D. NUTRITIONAL PRESCRIPTION

Indicate the body weight (BW) used in the calculation of nutritional targets*:

Tick appropriate block	Weight	Indication for use
	Actual BW	Underweight (at risk of *refeeding syndrome*)
	(Actual BW + ideal BW based on a BMI 18.5 kg/m^2) X 0.5	Underweight (no risk of *refeeding syndrome*)
	Actual BW	Normal weight
	Ideal BW	Overweight
	(Actual BW – ideal BW) X 0.25} + ideal BW	Obese
	BW used for calculations not charted, specify:	

Prescribed route of nutrition therapy at initial assessment by doctor/RD*:

☐ **EN** ☐ **PN** ☐ **EN & PN**

If EN, indicate route (tick appropriate block):

	Nasogastric		Orogastric
	Gastrostomy/PEG		Jejunostomy
	Other,specify:_____		

If PN, indicate access route (tick appropriate block):

	Central		Peripheral

When was nutrition therapy first initiated?*

☐ Initiated prior to ICU admission

☐ Initiated in ICU: Date (YYYY-MM-DD):_____ Time: (HH:MM, 24 hr)_____

Indicate initial route of nutritional therapy (tick appropriate block)*:

	EN		PN		Combination of EN & PN

Comments:_____

_____

_____

Calculation of nutritional targets (Use extra copies of this sheet as needed)					
Date	**Energy***	**PROT***	**HO**	**Lipid**	**Feeding script**
Date: _____ Day of ICU stay: _____ Responsible person: _____					Product*: _____ Volume/24hr*: _____ Rate/hr*:_____ **Prescribed energy intake (kcal/day):** _____ **Prescribed protein intake (g/day):** _____
Date: _____ Day of ICU stay: _____ *Reason for changing prescription:* _____ Responsible person: _____					Product*: _____ Volume/24hr*: _____ Rate/hr:*_____ **Prescribed energy intake (kcal/day):** _____ **Prescribed protein intake (g/day):** _____
Date: _____ Day of ICU stay: _____ *Reason for changing prescription:* _____ Responsible person: _____					Product*: _____ Volume/24hr*: _____ Rate/hr:*_____ **Prescribed energy intake (kcal/day):** _____ **Prescribed protein intake (g/day):** _____
Date: _____ Day of ICU stay: _____ *Reason for changing prescription:* _____ Responsible person: _____					Product*: _____ Volume/24hr*: _____ Rate/hr*:_____ **Prescribed energy intake (kcal/day):** _____ **Prescribed protein intake (g/day):** _____

E. PROGRESS REPORT	
Date	**Follow-up notes**

Appendix III: APACHE II scoring system

(Part of standardised data collection protocol)

The APACHE II severity of disease classification system:

	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (rectal)	>40.9	39-40.9		38.5-38.9	36.38.4	34-35.9	32-33.9	30-31.9	<30
Mean arterial pressure (mmHg)	>159	130-159	110-129		70-109		50-69		<50
Heart rate (ventricular)	>179	140-179	110-139		70-109		55-69	40-54	<40
Respiratory rate	>49	35-49		25-34	12-24	10-11	6-9		<6
Oxygenation FiO_2 <0.5 record Pa-O_2 FiO_2 >0.5 record A-aDO_2	>499	350-499	200-349		>70 <200	61-70		55-60	<55
Arterial pH	>7.69	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
If no ABG – serum HCO_3 (mmol/L)	>51.9	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15
Serum Sodium (mmol/L)	>179	160-179	155-159	150-154	130-149		120-129	111-119	<111
Serum Potassium (mmol/L)	>6.9	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Serum Creatinine (umol/L) Double score for acute renal failure	>299	170-299	130-169		50-129		<50		
Haematocrit (%)	>59.9		50-59.9	46-49.9	30-45.9		20-29.9		<20
White cell count ($1000/m^3$)	>39.9		20-39.9	15-19.9	3-14.9		1-2.9		<1

Total score = (15 – GCS) + APACHE score + Age points + Chronic health points

APACHE II SCORE = + + + =_____

Age points:

Age (years)	*Points*
<45	0
45-55	2
55-64	3
65-74	5
>74	6

Chronic health points:

If a patient has a history of severe organ system insufficiency or is immune-compromised assign points as follows:

g. For non-operative or emergency post-operative patients -> 5 points
h. For elective post-operative patients -> 2 points

Definitions:

Organ insufficiency or immune-compromised state must have been evident prior to this hospital admission and conform to the following criteria:

- Liver: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GIT bleeding attributed to portal hypertension.
- Cardovascular: New York Heart Association Class IV
- Respiratory: Chronic Restrictive, Obstructive, or Vascular disease resulting in severe exercise restriction, i.e. unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40mmHg), or respiratory dependency.
- Renal: Receiving chronic dialysis
- Immuno-compromised: the patient has received therapy that suppresses resistance to infection, e.g. Immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advances to suppress resistance to infection, e.g. leukaemia, lymphoma and AIDS.

Appendix IV
Daily Fluid & Nutritional Flow Chart

(Part of standardised data collection protocol)

Patient No:

DAILY FLUID AND NUTRITIONAL DATA*

Research No:

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	ICU Bed no:_____ Date:_____	ICU Bed no:_____ Date:_____	ICU Bed no:_____ Date:_____	ICU Bed no:_____ Date:_____	ICU Bed no:_____ Date:_____	ICU Bed no:_____ Date:_____	ICU Bed no:_____ Date:_____

1. INTRAVENOUS

1.1.Fluid support

1.1.1 Crystalloids

☐ Y ☐ N

Specify below:

Type:	Volume/ 24h (L):

1.1.2 Colloids

☐ Y ☐ N

Specify below:

Type:	Volume/ 24h (L):

1.1.3. Blood products

☐ Y ☐ N

Specify below:

Type:	Volume/ 24h (L):

DAILY FLUID AND NUTRITIONAL DATA

Pt No:

Research No:

	Day 1 Date:_____	Day 2 Date:_____	Day 3 Date:_____	Day 4 Date:_____	Day 5 Date:_____	Day 6 Date:_____	Day 7 Date:_____
1.2. IV drug & supplement dilution (*Obtain this data from the Daily IV Drug & Supplement Dilution Data Form)							
	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N
	Specify below:	Specify below:	Specify below:	Specify below:	Specify below:	Specify below:	Specify below:
	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):
1.3. Flushing of IV lines							
	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N
	Specify below:	Specify below:	Specify below:	Specify below:	Specify below:	Specify below:	Specify below:
	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):
1.4. IV electrolyte supplements							
	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N
	Specify below:	Specify below:	Specify below:	Specify below:	Specify below:	Specify below:	Specify below:
	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):
1.5. Nutritional prescription							
1.5.1. PN	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N
	Specify below:	Specify below:	Specify below:	Specify below:	Specify below:	Specify below:	Specify below:
	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):	Type: / Volume/ 24h (L):

DAILY FLUID AND NUTRITIONAL DATA

Pt No:

Research No:

	Day 1 Date:_____		Day 2 Date:_____		Day 3 Date:_____		Day 4 Date:_____		Day 5 Date:_____		Day 6 Date:_____		Day 7 Date:_____	
1.5.2 Dipeptivan	☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N	
	Specify below:		Specify below:		Specify below:		Specify below:		Specify below:		Specify below:		Specify below:	
	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):
1.5.3. Vitamin/ trace element suppl.	☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N	
	Specify below:		Specify below:		Specify below:		Specify below:		Specify below:		Specify below:		Specify below:	
	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):
1.6. Other (e.g. propofol; dextrose water infusion for hypoglycaemia)														
	☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N	
	Specify below:		Specify below:		Specify below:		Specify below:		Specify below:		Specify below:		Specify below:	
	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):
2. ENTERAL														
2.1 EN	☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N	
	Specify below:		Specify below:		Specify below:		Specify below:		Specify below:		Specify below:		Specify below:	
	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):

DAILY FLUID AND NUTRITIONAL DATA

Pt No:

Research No:

	Day 1 Date:_____		**Day 2** Date:_____		**Day 3** Date:_____		**Day 4** Date:_____		**Day 5** Date:_____		**Day 6** Date:_____		**Day 7** Date:_____	
2.2. Flushing of Feeding tube	☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N	
	Specify below:		Specify below:		Specify below:		Specify below:		Specify below:		Specify below:		Specify below:	
	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):
2.3. Other (e.g. vitamin/ trace element suppl; mixing crushed meds with water)	☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N	
	Specify below:		Specify below:		Specify below:		Specify below:		Specify below:		Specify below:		Specify below:	
	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):	Type:	Volume/ 24h (L):
3. ORAL														
3.1. Nutrition	☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N	
	Specify below:		Specify below:		Specify below:		Specify below:		Specify below:		Specify below:		Specify below:	
	Purpose:	Volume/ 24h (L):	Purpose:	Volume/ 24h (L):	Purpose:	Volume/ 24h (L):	Purpose:	Volume/ 24h (L):	Purpose:	Volume/ 24h (L):	Purpose:	Volume/ 24h (L):	Purpose:	Volume/ 24h (L):
3.2. Other (incl. water)	☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N		☐ Y ☐ N	
	Specify below:		Specify below:		Specify below:		Specify below:		Specify below:		Specify below:		Specify below:	
	Purpose:	Volume/ 24h (L):	Purpose:	Volume/ 24h (L):	Purpose:	Volume/ 24h (L):	Purpose:	Volume/ 24h (L):	Purpose:	Volume/ 24h (L):	Purpose:	Volume/ 24h (L):	Purpose:	Volume/ 24h (L):

Appendix V:

Standardised procedure for drug administration & IV line flushing

(Part of standardised data collection protocol)

Standardised procedure for drug administration & IV line flushing

1. IV LINE FLUSHING

a. Automatic flush

A heparin-saline solution (hep-saline) is routinely used for the flushing of IV lines. Hep-saline consists of a 1000 IU (1ml) of heparin added to 999ml of normal saline to allow a 1:1 titration. The "infusible pressure bag" is maintained at a constant pressure of 300mmHg to allow an automatic hep-saline flush of 3ml/hr.

b. Manual flush

Arterial lines are manually flushed with approximately 5ml of hep-saline after administration of "push-in" drugs, including the "push-in" administration of insulin (sliding scale).

2. RECONSTITUTION OF POWDERED DRUGS PRIOR TO INTRAVENOUS ADMINSTRATION

Sterile saline is routinely used for the reconstitution of powdered drugs, except for drugs with its own reconstitution liquid enclosed in its packaging.

3. IV DRUG DILUTION

a. Type of diluent

- Drugs are mixed with normal saline, unless:
    - A given drug is incompatible with normal saline
    - A patient's serum sodium level exceeds 149mmol/L, in which case 5% dextrose water is used for drug dilution (unless the given drug is incompatible with 5% dextrose water).
- The following drugs are routinely mixed with 5% dextrose water:
    - Amphotericin B
    - Amiodarone
- The following drugs are strictly mixed with normal saline only:
    - Epanutin

b. Diluent volume

- Adding drugs to a saline/dextrose water bag:

It is a fixed unit protocol for the prescribed drug volume to be removed from the given diluent's IV bag prior to adding the drug (e.g. remove 12ml from a 200ml normal saline bag before adding 12 amps adrenaline). The assumption was therefore made that all drugs were routinely mixed according to this procedure.

– Antimicrobial committee antibiotic injection guidelines:

All “push-in” drugs must be diluted in 10ml sterile saline unless otherwise stated and given through a freely running IV line over a period of not less than 3 minutes:
Aminoglycosides, Amikacin, Tobramycin, Gentamycin, Cephalosporins (incl Cefazolin, Cefuroxime, Cefotaxime, Ceftriaxone, Ceflazidime), Cephamycins (incl Cefozitin, Penicillin, Ampicillin, Cloxacillin, Amoxid)

Drugs indicated as “per protocol” should not be given as “push in”. Check package insert for a precise administration policy. Some of these drugs require specific dilution or are pre-diluted by the manufacturer and require a specific infusion time:
Amphotericin B, Ciprofloxacillin, Clindamycin, Diethanolamine, Fusidate, Erythromycin, Imipenem, Meropenem, Ofloxacin, Piperacillin, Tazobactam, Vancomycin

If the flushing of IV lines, reconstitution of powdered drugs or drug dilution are inaccurately charted by the nursing staff, a standardised procedure (Table 1) will be followed to estimate the given fluid volume. This standardised procedure is based on the precise administration policy as indicated on the package insert or on standard ICU protocols for the administration of drugs.

4. STANDARDISED PROCEDURE FOR THE ADMINISTRATION OF DRUGS VIA AN ENTERIC TUBE

a. Drugs in tablet form:

– Drugs are crushed and mixed with approximately 10ml of water prior to administration.

b. Drugs in liquid form:

– Ulsanic: 5ml = 1 gram

–Tegretol: 5ml = 500mg

The enteric tube is flushed with approximately 10ml of water after the administration of drugs.

5. STANDARDISED PROCEDURE FOR SWALLOWING OF TABLETS

The assumption is made that tablets are swallowed with approximately 30ml of water

Table 1: Intravenous drug administration

Drug			Method	Often prescribed dose	Reconstitution		Dilution		NS flush
Name	**Form**	**Grams/volume**			**Fluid**	**Volume**	**Diluent**	**Volume**	**Volume**
Analgesics/sedatives									
Morphine	Liquid	1ml amp = 15mg	Push	1 - 4 mg prn	NS	15mg (1ml) to 14ml (1:1 titration)	None	None	5ml
			CI	As prescribed	None	None	NS/D5W	45mg (3ml) to 47ml (1:1 titration)	None
Serenace	Liquid	2ml amp = 20mg	Push	2.5/5mg tds	None	None	None	None	5ml
Dormicum	Liquid	3ml = 15mg	Push	1 - 4mg prn	NS	15mg (3ml) to 12ml (1:1 titration)	None	None	5ml
			CI	As prescribed	None	None	NS/D5W	100mg (10ml) to 90ml (1:1 titration)	None
Tramadol/Tramal	Liquid	2ml amp = 100mg	Push	50mg bd	None	None	None	None	5ml
Ampicilllin/Ranamp	Powder	1 vial = 500mg	IM	250mg/500mg/1g	None	None	NS/D5W	50ml	None
Phenergen/Promethazine HCl	Liquid	1ml amp = 25mg	Push	As prescribed	None	None	None	None	5ml
Perfalgon	Liquid	100ml bottle = 1g	IM	1g tds/qid	None	None	None	None	None
Ulcer prohylaxis									
Pantoloc	Powder	1 vial = 40/80mg	IM	40mg dly/bd/tds	NS	10ml	NS/D5W	50ml	None
			CI	40mg/80mg dly	None	None	NS/D5W	Add prescribed dose to 200ml, run at 8ml/hr	None
Antithrombotic									
Heparin	Liquid	1ml amp = 1000/5000IU	CI	As prescribed	None	None	NS only	Add amount of heparin to be given per hour X 12 to 100mls minus heparin volume, run at 8ml/hr over 12 hours	None

Table 1: Intravenous drug administration

Drug			Method	Often prescribed dose	Reconstitution		Dilution		NS flush
Name	**Form**	**Grams/volume**			**Fluid**	**Volume**	**Diluent**	**Volume**	**Volume**
Corticosteroids									
Solucortef	Powder	1 vial = 100mg	Push	100mg tds/qid	NS	2ml	None	None	5ml
Solumedrol	Powder	1 vial = 40/125/500mg	Push	500mg dly	WFI	500mg to 8ml	None	None	5ml
Decadron	Liquid	4ml Amp = 8mg	Push	8mg tds	None	None	None	None	5ml
Prokinetics									
Maxolon/Metoclopramide	Liquid	2ml amp = 10mg	Push	10 mg tds	None	None	None	None	5ml
Erythromycin	Powder	1 vial = 1g	IM	250mg tds/1g dly	NS	5ml	NS/D5W	50ml	None
Diuretics									
Lasix/Furosemide	Liquid	2ml amp = 20mg	Push	5mg tds	None	None	None	None	5ml
			CI	As prescribed	None	None	NS/D5W	100mg (10ml) to 90ml (1:1 titration)	None
Neuro-related drugs									
Rivotril	Powder	1 vial = 1g	Push	1g tds	Own SW	2ml	None	None	5ml
Epilim/ Sodium Valproate	Powder	1 vial = 400mg	IM	400mg tds	Own SW	4ml (total volume= 5ml)	NS/D5W	100ml	None
Epanutin/Phenytoin	Liquid	5ml Amp = 250mg	IM	300mg/750mg/1g	None	None	**Only NS**	50/100/100	None
			CI	As prescribed	None	None	**Only NS**	200ml minus drug volume	None
Muscle relaxants									
Vencuronium bromide/ Norcuron	Powder	1 vial = 10mg	Push	20mg stat for intubation	NS	5ml (hence 2mg/ml)	None	None	5ml
Pancuronium bromide/ Pavulon	Liquid	2ml amp = 40mg	Push	As prescribed	None	None	None	None	5ml
Etomidate	Liquid	5ml amp = 10mg	Push	10mg for intubation	None	None	None	None	5ml

Table 1: Intravenous drug administration

Drug			Method	Often prescribed dose	Reconstitution		Dilution		NS flush
Name	**Form**	**Grams/volume**			**Fluid**	**Volume**	**Diluent**	**Volume**	**Volume**
Glucose control									
Actrapid/Humulin R	Liquid	1ml = 100U	Push	Sliding scale	NS	2ml	None	None	5ml
			CI	As prescribed	None	None	NS/D5W	1ml (100U) to 99ml	None
Cardiac-related drugs									
Digoxin/Lanoxin	Liquid	2ml amp = 0.5mg	Push	As prescribed	None	None	None	None	5ml
Inotropic support									
Dobutrex*	Liquid	20ml amp = 250mg	CI	APP	None	None	NS/D5W	1g (80ml) in 120ml	None
Adrenaline*	Liquid	1ml amp = 1mg	CI	APP	None	None	NS/D5W	6 amps (6ml) to 194ml	None
								12 amps (12ml) to 188ml	None
								24 amps (24ml) to 176ml	None
								48 amps (48ml) to 152ml	None
Phenylephrine*	Liquid	1 ml amp = 10mg	CI	APP	None	None	NS/D5W	10 mg (1 amp) to 199 ml	None
								40mg (4ml) to 196ml	None
								80mg (8ml) to 192ml	None
Amiodarone/Corderone*	Liquid	3ml = 150mg	CI	600/1200mg	None	None	**Only D5W**	Loading dose: 5mg/kg in 100ml over 30min	None
								Then 1200mg over 24 hrs: Add 600mg (4 amps) to 188ml, run at 17ml/hr over 12hrs	None

Table 1: Intravenous drug administration

Drug			Method	Often prescribed dose	Reconstitution		Dilution		NS flush
Name	**Form**	**Grams/volume**			**Fluid**	**Volume**	**Diluent**	**Volume**	**Volume**
Antibiotics									
Ampicillin	Powder	1 vial = 500mg	Push	250mg/500mg/1g	NS	10ml	None	None	5ml
Amikacin	Liquid	2ml vial = 500mg	Push	500mg/1000mg dly	NS	10ml	None	None	5ml
			IM	500mg/1000mg dly	None	None	NS/D5W	50/100ml	None
Augmentin	Powder	600mg/1200mg	IM	600/1200mg tds	None	None	NS/D5W	50ml	None
Azithromycin/Zithromax	Powder	1 vial = 500mg	IM	500mg dly/bd	Own SW	4.8ml (Total volume= 5ml)	NS/D5W	100ml (50ml if RF)	None
Bactrim	Liquid	1 amp = 3ml	IM	4 amps (12ml) qid	None	None	NS/D5W	4 amps (12ml) to 38ml	None
Clarithromycin/Klacid	Powder	1 vial = 500mg	IM	As prescribed	None	None	NS/D5W	100ml	None
Cefazolin/Ranzol/Kefzol/ Keftaz	Powder	1 vial = 1g	Push	500mg/1g/2g dly	NS	10ml	None	None	5ml
			IM	500mg/1g/2g dly	None	None	NS/D5W	50ml	None
Cefepime/Maxapime	Powder	1 vial = 500mg/1g/2g	IM	As prescribed	None	None	NS/D5W	50ml	None
			CI	3g/4g dly	None	None	NS/D5W	3g to 100ml/4g to 200ml, run at 12.5 ml/hr	None
Cefotaxime Na/ Claforan/Tazocef	Powder	1 vial = 1g	Push	500mg/1g bd	NS	10ml	None	None	5ml
			IM	500mg/1g bd	None	None	NS/D5W	50ml	None
Ceflazidime/Taziject	Powder	500mg/1g/2g	Push	As prescribed	NS	10ml	None	None	5ml
			IM	As prescribed	None	None	NS/D5W	50ml	None
Rocephin/Ceftriaxone/Kocef-1000	Powder	250mg/500mg/1g	Push	250mg/500mg/1g bd	NS	10ml	None	None	5ml
			IM	250mg/500mg/1g bd	NS	5ml/5ml/10ml	NS/D5W	50/50/100ml	None
Cefuroxime/Zinacef	Powder	1 vial = 750mg	Push	750mg qid	NS	10ml	None	None	5ml
			IM	750mg qid	None	None	NS/D5W	50ml	None
Cimetidine/Ranitidine/Zantac	Liquid	2ml amp = 50mg	IM	150mg bd	None	None	NS/D5W	50ml	None

Table 1: Intravenous drug administration

Drug			Method	Often prescribed dose	Reconstitution		Dilution		NS flush
Name	Form	Grams/volume			Fluid	Volume	Diluent	Volume	Volume
Ciprofloxacillin/Ciprobay/ Ciprocina	Liquid	100ml bottle = 200mg	IM	200mg dly	None	None	None	None	None
Clindamycin	Liquid	4ml amp = 600mg	IM	300/600/900/1200mg/d	None	None	NS/D5W	50/100/150/200ml	None
Cloxacillin	Powder	1 vial = 500mg	Push	As prescribed	NS	10ml	None	None	5ml
			IM	As prescribed	None	None	NS/D5W	50ml	None
Ertapenem	Powder	1 vial = 1g	IM	500mg bd	None	None	NS/D5W	50ml	None
Flagyl	Liquid	100ml bottle = 500mg	IM	500mg tds	None	None	None	None	None
Gentamycin	Liquid	2ml amp = 80mg	IM	80/120mg dly	None	None	NS/D5W	50ml	None
Imipenem	Powder	1 vial = 500mg	IM	1g tds	None	None	NS/D5W	100ml	None
Linezolid/zyvoxid	Liquid	300ml bag = 600mg	IM	600mg tds	None	None	NS/D5W	50ml	None
Meropenem	Powder	1 vial = 500mg/1000mg	IM	250/500/1000mg dly	None	None	NS/D5W	50ml	None
Tazocin/Piptaz	Powder	1 vial = 4.5g	IM	4.5g	None	None	NS/D5W	50ml	None
			CI	9/18g dly	None	None	NS/D5W	200ml	None
Tobramycin	Liquid	2ml amp = 80mg	Push	240mg bd	NS	10ml	None	None	5ml
			IM	240mg bd	None	None	NS/D5W	50ml	None
Teicoplanin/Targocid 200	Liquid	10ml vial = 200mg	IM	As prescribed	None	None	NS/D5W	50ml	None
Vancomycin	Powder	1 vial = 500mg/1g	IM	500mg/1g stat	None	None	NS/D5W	50ml/100ml	None
			CI	2g dly	None	None	NS/D5W	2g to 200ml, run at 8ml/hr	None
Antifungal									
Amphothericin B/Fungizone*	Powder	1 vial = 50mg	CI	40mg dly	None	None	D5W only	40mg to 200ml, run at 8ml/hr	None

Table 1: Intravenous drug administration

Drug			Method	Often prescribed dose	Reconstitution		Dilution		NS flush
Name	**Form**	**Grams/volume**			**Fluid**	**Volume**	**Diluent**	**Volume**	**Volume**
Fluconazole	Liquid	100ml bottle = 200mg	IM	200mg tds	None	None	None	None	None
Voriconazole	Powder	1 vial = 200mg	IM	600mg dly	None	None	NS/D5W	50ml	None
Antiviral									
Acyclovir/Zovirax	Powder	1 vial = 250mg	IM	As prescribed	None	None	NS/D5W	100ml	None
Glanciclovir/Cymevene	Powder	1 vial = 500mg	IM	250mg tds	None	None	NS/D5W	100ml	None
Metronidazole	Liquid	100ml bag = 500mg	IM	As prescribed	None	None	None	None	None
Antiprotozoal									
Artesunate/Artesun	Powder	1 vial = 60mg	IM	As prescribed	Own 5% NaHCO3	1 ml (Total volume = 6ml)	NS/D5W	50ml	None
Quinine	Liquid	1 ml amp = 300mg	CI	As prescribed	None	None	D5W only	600mg (2ml) to 198ml	None
Antifibrinolytic									
Cyclokapron	Liquid	5ml amp = 500mg	IM	500mg tds	None	None	NS/D5W	50ml	None
Other									
Acetylcysteine/Parvolex	Liquid	10ml amp = 2g	IM	600mg (3ml) tds	None	None	NS/D5W	50ml	None
			CI	As prescribed	None	None	NS/D5W	200ml minus drug volume, run at 8ml/hr	None
Lignocaine	Liquid	5ml amp = 0.1g	IM	As prescribed	None	None	NS/D5W	50ml	None
Salbutamol	Liquid	5ml amp = 5mg	Push	5mg/10mg	NS	5ml	None	None	5ml
Aminophylline	Liquid	10ml amp = 250mg	IM	175mg (7ml) stat	None	None	NS/D5W	43ml	None
				400mg (16ml) stat	None	None	NS/D5W	84ml	None
			CI	1g dly	None	None	NS/D5W	1g (40ml) to 160ml	None

Table 1: Intravenous drug administration

Drug			Method	Often prescribed dose	Reconstitution		Dilution		NS flush
Name	Form	Grams/volume			Fluid	Volume	Diluent	Volume	Volume
TNT/Nitroglycerine*	Liquid	10ml = 25mg	CI	APP	None	None	NS/D5W	50mg (20ml) to 180ml, run at 8ml/hr	None
Precedex/Dexmedetomidine	Liquid	2ml amp = 200mcg	CI	APP	None	None	NS/D5W	1 amp (2ml) to 48ml, run at 1 - 18ml/hr	
Atropine*	Liquid	10ml amp = 10mg	CI	APP	None	None	NS/D5W	10mg (10ml) to 190ml (1:1 titration)	None
		1ml amp = 0.5mg	CI	APP	None	None	NS/D5W	10mg (20ml) to 180ml diluent (1:1 titration)	None
DDAVP*	Liquid	1ml amp = 4mcg	CI	APP	None	None	NS/D5W	6 amps (6ml) to 194ml	None
Trandate/Labatol	Liquid	1 ml amp = 5mg	CI	As prescribed	None	None	NS/D5W	200mg (40ml) to 160ml	None
Haemosolvex Factor IX	Powder	1 vial =500 IU	Push	As prescribed	Own WFI	10ml	None	None	5ml
Polygam	Powder	6g/12g/24g	CI	As prescribed	None	None	Own NS	6g to 200ml/12g to 400ml/24g to 800ml	None
Propofol 1%	Liquid	10mg/ml	CI	As prescribed/APP	None	None	None	None	None
Robinul	Liquid	1ml amp = 0.2mg	CI	APP	None	None	NS/D5W	10 amps (10ml) to 190ml, run at 10ml/hr	None
Ketamine*	Liquid	10ml vial = 1000mg	CI	As prescribed	None	None	NS/D5W	10mg (0.1ml drug) to 30ml (induction dose)	None
								50mg (0.5ml drug) to 49.5ml	None
								100mg (1ml drug) to 99ml	None
								150mg (1.5ml drug) to 148.5ml	None
								400mg (4ml) to 196ml	None
Somatostatin*	Liquid	1ml amp = 0.05mg/0.1mg	CI	APP	None	None	NS/D5W	10 amps (10ml) to 190ml, run at 10ml/hr	None
Remifentanyl/Ativan	Liquid	1ml amp = 2mg	C	APP	None	None	NS/D5W	2mg (1ml) to 49ml	None

Table 1: Intravenous drug administration

Drug			Method	Often prescribed dose	Reconstitution		Dilution		NS flush
Name	**Form**	**Grams/volume**			**Fluid**	**Volume**	**Diluent**	**Volume**	**Volume**
Electrolyte supplementation									
Potassium chloride 15%	Liquid	10ml amp = 1.5g	IM	APP	None	None	NS/D5W	20mmol (10ml) to 50ml	None
								40mmol (20ml) to 100ml	None
								60mmol (30ml) to 150ml	None
Potassium phosphate	Liquid	10ml amp = 2.14g	IM	APP	None	None	NS/D5W	20mmol (10ml) to 50ml	None
								40mmol (20ml) to 100ml	None
								60mmol (30ml) to 150ml	None
Calcium chloride 10%	Liquid	10ml amp = 1g	IM	10ml stat	None	None	NS/D5W	10ml to 50ml	None
Calcium gluconate 10%	Liquid	10ml amp	IM	10ml stat	None	None	NS/D5W	10ml to 50ml	None
Magnesium sulphate	Liquid	2ml = 1g	IM	2g (4ml) stat	None	None	NS/D5W	2g (4ml) to 100ml	None
				10g	None	None	NS/D5W	10g (20ml) to 180ml, run at 20ml/hr	None
Sodium bicarbonate 8.5%	Liquid	50ml bag	IM	As prescribed	None	None	None	None	None
Vitamin supplementation									
Vitamin C	Liquid	5ml amp = 500mg	Push	1g dly	None	None	None	None	5ml
Vitamin K	Liquid	1ml amp = 10mg	Push	Once dly or bd	None	None	None	None	5ml
Thiamine	Liquid	10ml vial = 100mg	Push	100mg/300mg dly	None	None	None	None	5ml

*Dobutrex, adrenaline, phenylephrine, amiodarone, amphotericin B, TNT, Precedex, Atropine, DDAVP, Robinul, Ketamine, Somatostatin; Epidural protocol: Standard ICU protocols
Abbreviations: NS: Normal saline; IM: Intermittent infusion; CI: Continuous infusion; APP: As per protocol; D5W: 5% dextrose water; WFI: Water for injection.

APPENDIX C

GENERAL ICU (CMJAH) GUIDELINES FOR ADJUSTING WEIGHT FOR OEDEMA/AMPUTATIONS

GICU (CMJAH) GUIDELINES FOR ADJUSTING WEIGHT FOR FLUID RETENTION AND AMPUTATIONS

I. WEIGHT ADJUSTMENT FOR VISIBLE OEDEMA	
Degree of oedema	**Correction factor**
Mild	Actual/estimated body weight – 1 kg
Moderate	Actual/estimated body weight – 5 kg
Severe	Actual/estimated body weight – 10 kg
II. WEIGHT ADJUSTMENT FOR AMPUTATIONS	
Body Part	**Contribution to body weight (%)[A]**
Entire arm	6.5
Upper arm	3.5
Forearm	2.3
Hand	0.8
Entire leg	18.5
Upper leg	11.6
Lower leg	5.3
Foot	1.8
Adjusted BW = (Estimated or current body weight/100 - % of amputation) X 100	

APPENDIX D

PRE-STUDY NURSING STAFF TRAINING HAND-OUT

576 GENERAL ICU (CMJAH) CLINICAL NUTRITION RESEARCH	
GENERAL INFORMATION	
Research Study:	The Impact of Intravenous Fluid and Electrolyte Administration on Total Fluid, Electrolyte and Energy intake in Critically Ill Adult Patients.
Investigator:	Lizl Veldsman
Co-investigators:	Prof GA Richards Prof R Blaauw
Contact details	Lizl Veldsman c: +2782 414 5084 w: (011) 488 4348 lizlveld@gmail.com
AIM & OBJECTIVES	
AIM:	To determine the nutritional content / contribution of IV fluid and electrolyte administration on the total feeding prescription of ICU patients.
OBJECTIVES:	(1) To determine the volume and types of IV fluids most often prescribed to ICU patients. (2) To determine the IV electrolyte supplements (type and dosing) most often prescribed to ICU patients. (3) To determine the contribution of the following routine ICU practices to a patient's total fluid, electrolyte, energy and macronutrient intake: -Crystalloids, colloids and blood products used for **IV fluid and volume management** -Crystalloids used for **IV drug dilution** and **flushing of IV lines** -Lipids delivered with sedatives (***propofol***) -**IV electrolyte replacement** (4) To compare a patient's total energy and macronutrient intake with his/her individualized feeding prescription.
Data Collection	
Data will be collected retrospectively from the patients' ICU charts once they are discharged from ICU. The following data will be collected from the day of ICU admission until a maximum of 7 days: - **Type** and **volume** of IV fluids used for **fluid support** - **Type** and **volume** of IV fluids used for **IV drug dilution** - **Type** and **volume** of IV fluids used for **flushing of IV lines** - **Type** and **dosing** of IV electrolyte replacement (if prescribed) - **Dose** of **propofol and/or dipeptivan** infused (if prescribed) - **Type** and **volume** of **enteral and/or parenteral nutrition** delivered to the patient. - **Type** and **volume** of **fluids and/or feeds taken orally** (if applicable)	

This study is based on a **retrospective review of patients' ICU charts**.

THEREFORE the success of this study largely depends on how accurate patients' information is recorded on their ICU charts.

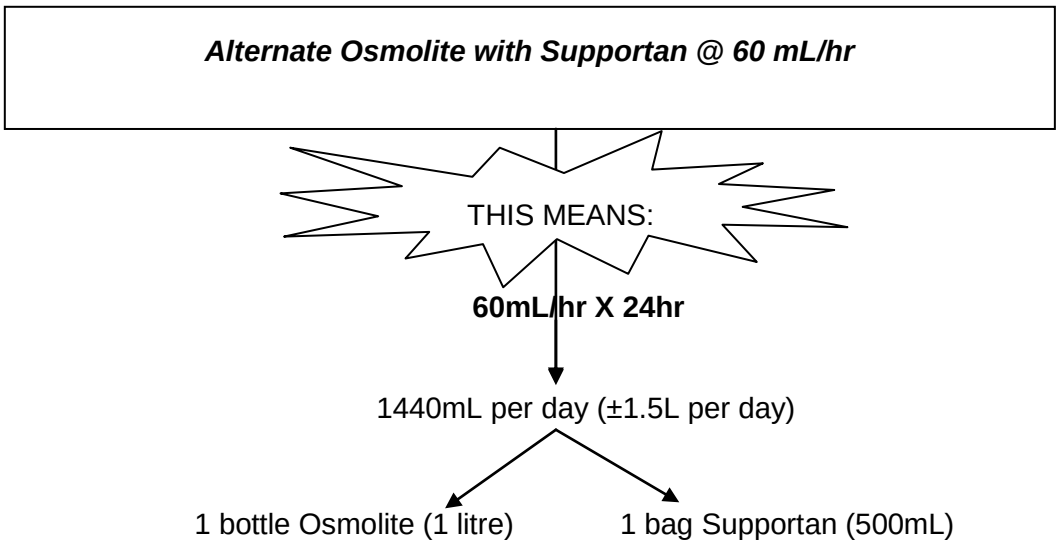
THEREFORE ALL OF YOU PLAY A CRUCIAL ROLE IN THE SUCCESS OF THIS STUDY!

Will you please ensure that the following information is accurately recorded on the ICU charts of all patients in ICU:

Arterial blood gas values **-** Haematocrit %
Fluid support: **-** Name of IV solution used (e.g. *Ringer's Lactate*) **-** Rate of administration (e.g. 80mL/hr)
IV drug dilution: Please chart the following information **every time an IV drug or -electrolyte (e.g. KCl) is diluted**: **-** Name of IV solution used (e.g. D5W, N/S) **NB: Please indicate if D5W was used instead of N/S.** **-** Volume used (e.g. 40mmoL KCL diluted in 200mL N/S)
Flushing of IV lines: Please chart the following every time an IV line is flushed: **-** NAME OF IV SOLUTION used for flushing IV lines (e.g. N/S) **NB: Please indicate if D5W was used instead of N/S.** **-** Approximate VOLUME used for flushing of IV lines (e.g. 3mL)
IV electrolyte administration: **-** Please indicate the TYPE (e.g. KCl, KPO_4) and DOSE (e.g. 40 mmol) administered.
Propofol/dipeptivan infusion: **-** If propofol or dipeptivan is prescribed to a patient, please chart the RATE at which it is administered to the patient.
Crushing of medications given via the NGT/OGT: **-** Please indicate the VOLUME (e.g. 10mL) of water mixed with the crushed meds. If a fluid other than water was used (e.g. saline), please chart what fluid has been used.

Enteral nutrition:

- Accurately chart the NAME OF THE FEED (e.g. Nutrison Low Sodium) and the RATE (e.g. 60mL/hr) OF ADMINISTRATION.
- If a patient's feeding prescription is changed (e.g. changed from Osmolite to Fresubin 1200 Complete), please indicate on the fluid chart the exact time at which the feed has been changed.
- If a patient's feeding prescription is as follows:



Parenteral nutrition

Please chart the following on the patient's ICU chart:

- The ITN regimen (e.g. ITN8004XA)
- Every time a new TPN bag is started, please record the name of the TPN bag (e.g. Kabiven or ITN8003XA) as well as the rate of infusion on the patient's ICU chart.

E.g. At 10h00 patient X is started on Kabiven @ 60mL/hr. At 17h00 that afternoon the Kabiven bag is discarded and the prescribed ITN bag (e.g. ITN 8804XA) is started.

Chart the following: *10h00 = KABIVEN 60mL/hr*
17h00 = ITN8804A 60mL/hr.

Oral feeds:

Accurately chart the type and volume of oral feeds taken in by the patient. This includes:

- Sips of water
- Tea
- Porridge
- Sipfeeds
- Jelly