INVESTIGATION OF DRUG NUTRIENT INTERACTIONS AND PHYSICOCHEMICAL COMPATIBILITIES OF CEFTAZIDIME, CEFOTAXIME AND CEFEPIME IN NEONATAL TOTAL NUTRIENT ADMIXTURES USING HPLC

By

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**Thesis submitted in fulfillment of the requirements
for the degree of
Doctor of Philosophy
(Clinical Pharmacy)**

August 2013

DEDICATION

To

My Father

For the Uncompromising Principles that Guided His Life

My Mother

For Leading Her Children into Intellectual Pursuits

My Brothers

For Making Everything Worthwhile

My Wife

For Her Insight, Patience and Unfailing devotion

To

My Teachers

For Showing Me the Excitement and Joy of Pharmacy

My Friends

For Their Abundant Support, For Their Patience
and Understanding and for Their Help.

Muhammad Shahid Iqbal

ACKNOWLEDGEMENT

All prayers for Almighty ALLAH, the most beneficent, the most merciful. After that heartiest gratefulness to the Holy Prophet Muhammad (SAW) who enlightened our soul with significance of identification yearning to inquest for the hidden. Indubitably sincerest gratitude goes to Sultan-Ul-Arifeen, Hazrat Sakhi Sultan Bahu (R.A) and Baba G (R.A) for all their nepotism and sustenance.

I would particularly like to express my deepest thanks to those who helped me in the completion of my thesis. I am also grateful to all my friends and colleagues who generously contributed their time and efforts to help me make this project possible.

I owe a special debt of gratitude to my supervisor **Dr. Mohd. Baidi Bin Bahari,** Associate Professor, Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, who thoroughly reviewed my thesis and help me a lot. No doubt, without his talented sense, kindheartedness and supervision, it was impossible for me to complete this journey.

I have no proper words to thank my co-supervisor **Dr. Yusrida Darwis,** Associate Professor, Department of Pharmaceutical Technology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, for her invaluable guidance, help and providing all the facilities throughout completion of this project. I am exceedingly grateful to her for this kindness.

I am also indebted to Dr. Mian Muhammad Zahid Iqbal, Dr. Venkatish, Dr. Khalid Hussain, Dr. Hassaan A. Rathore, Dr. Amer Hayat, Dr. Chitnaini Mallikarjun, Syed Haroon Khalid, Syed Wasif Gillani and Atiqah Mohtar, who also helped me during whole time by sparing their valuable time. I highly value the additional support of my other respected faculty teachers and my colleagues who have encouraged me a lot during my whole work.

Muhammad Shahid Iqbal

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LIST OF ABBREVIATIONS

AIO TPN	All in one TPN
ASCN	American society for clinical nutrition
ASPEN	American society of parenteral and enteral nutrition
CV	Coefficient of variation
ESPEN	European society of parenteral and enteral nutrition
ELBW	Extremely low birth weight
FFA	Free fatty acids
HPLC	High performance liquid chromatography
HUSM	Hospital Universiti Sains Malaysia
IVPB	Intravenous Piggyback
ICH	International conference on harmonization
ISABs	Ionic strength adjustment buffers
ISEs	Ion selective electrodes
LOD	Limit of detection
LOQ	Limit of quantification
PN	Parenteral nutrition
PHLA	Post heparin lipolytic activity
TPN	Total parenteral nutrition
TNAs	Total nutrient admixtures
TIO TPN	Two in one TPN

LIST OF ANNEXURES

KAJIAN INTERAKSI DRUG-NUTRIEN SERTA KESERASIAN FIZIKOKIMIA SEFTAZIDIM, SEFOTAKSIM DAN SEFEPIM DALAM ADMIKSTUR NUTRIEN NEONAT TOTAL MENGGUNAKAN HPLC

ABSTRAK

Campuran keseluruhan nutrient (TNA) teleh digunakan secara meluas sebagai kaedah terapeutik dalam pengurusan pesakit kekurangan zat makanan yang menerima nutrisi parenteral sejak kelulusan untuk mencampur emulsi lemak intravena dengan pelbagai larutan asid amino dan dekstrosa. Kelebihan TNAs termasuk rawatan nutrisi dirumah, kurang risiko jangkitan, memerlukan kurang kakitangan kejururawatan, tidak memerlukan tambahan bendalir untuk mencairkan drug, penurunan kos pemberian berbanding dengan kaedah piggyback konvensional dan peningkatan toleransi intravena emulsi lemak dalam neonat. Penambahan antibiotik ke dalam TNAs sering menimbulkan persoalan mengenai kestabilan antibiotik untuk tempoh yang lebih lama, seperti 24 jam. Malangnya, data mengenai kesetabilan TNAs di dalam/dengan antibiotik jarang diperolihi. Kajian ini bertujuan untuk menilai kestabilan dan keserasian antibiotik (ceftazidime, cefepime dan cefotaxime) dalam TNAs. Kesetabilan dan keserasian diukur secara kimia menggunakan HPLC berkelajuan tinggi (Prominence UFLC model LC-20AD, Shimadzu, Columbia, Amerika Syarikat) menggunakan kaedah yang dibangunkan sendiri dan telah disahkan. Jangka hayat dan peratusan antibiotik yang masih ada dalam semua formulasi / sampel diukur pada selang masa yang berbeza (H0, H4, H8, H16 dan H24) dengan menggunakan kaedah di atas. Kepekatan komponen TNAs seperti makronutrien dan mikronutrien yang digunakan dalam kajian ini adalah mengikut berat badan normal neonat iaitu 3 kg. Kajian ini menilai kesan pelbagai kepekatan makronutrien tersebut dalam / dengan antibiotik. Setiap antibiotik, 48 formulasi TNAs telah disediakan dalam kombinasi makronutrien

(dekstrosa, asid amino dan lemak) dan mikronutrien (vitamin, elektrolit dan unsur surih) yang berbeza. Kesetabilan formulasi telah dinilai bagi parameter fiziko-kimia seperti pH, saiz titisan, potensi zeta, pemendakan, pembekuan, penggumpalan dan kepekatan natrium, kalium serta kepekatan drug. Kajian ini telah dijalankan pada suhu bilik (25 ± 2°C) dan sampel telah dikumpulkan pada 0, 4, 8, 16 dan 24 jam masing-masing. Kepekatan antibiotik dalam sampel dianalisis dengan menggunakan kaedah HPLC yang telah disahkan di atas. Kajian mendapati ceftazidime dan cefepime stabil sehingga 16 jam manakala cefotaxime pada stabil sehingga 24 jam di semua formulasi TNAs dan seterusnya meluluh melebihi daripada 10% masing-masing. Hasil keserasian fiziko-kimia menunjukkan bahawa tidak terdapat sebarang perubahan signifikan dalam pH, saiz titisan, potensi zeta dan kepekatan natrium dan kalium dalam semua sediaan (semua $p \geq 0.05$). Di samping itu, tidak terdapat pembekuan dan pemendakan signifikan diperhatikan dalam tempoh tersebut. Kesimpulannya, kajian ini menunjukkan bahawa ceftazidime dan cefepime adalah serasi dan stabil selama 16 jam di dalam / dengan TNAs manakala cefotaxime serasi dan stabil selama 24 jam di dalam / dengan TNAs.

INVESTIGATION OF DRUG NUTRIENT INTERACTIONS AND PHYSICOCHEMICAL COMPATIBILITIES OF CEFTAZIDIME, CEFOTAXIME AND CEFEPIME IN NEONATAL TOTAL NUTRIENT ADMIXTURES USING HPLC

ABSTRACT

Total nutrient admixtures (TNAs) is widely used therapeutic intervention in the management of malnourished patients receiving parenteral nutrition since the approval of admixing intravenous fat emulsions with various amino acids and dextrose solutions. The advantages of TNAs include home nutrition therapy, less risk of infections, less need of nursing staff, no need of additional fluids to dilute the drugs, decreased administration costs compared with the conventional piggyback method and increased tolerance of intravenous fat emulsions in neonates. Addition of antibiotics to the TNAs often raises question of stability of the antibiotics over longer periods e.g. 24 hours. Unfortunately, very little data about TNAs stability in/with antibiotics is available. This study was aimed to evaluate the stability and compatibility of antibiotics (ceftazidime, cefepime and cefotaxime) in TNAs. The stability and compatibility were measured chemically, by using a high-speed HPLC (Prominence UFLC model LC-20AD, Shimadzu, Columbia, USA) based on newly developed and validated methods. Shelf life and percentage of remaining antibiotics in all formulations were measured at different time intervals (H0, H4, H8, H16 and H24) by using the above methods. The concentrations of TNAs' components i.e. macronutrients and micronutrients used in the study were according to the normal body weight of neonates i.e. 3 kg neonates. The study evaluated the effect of varied concentrations of macronutrients in/with antibiotics. For each antibiotic, forty-eight TNAs formulations were prepared in different combinations of macronutrients (dextrose, amino acids and fats) and micronutrients (vitamins,

and trace elements). The stability of the formulations were evaluated for various physico-chemical parameters such as pH, globule size, zeta potential, precipitation, flocculation, coalescence and concentrations of sodium, potassium and drug concentrations. The experiments were carried out at room temperature (25±2°C) and samples were collected at 0, 4, 8, 16 and 24 hours respectively. Antibiotic concentrations in the samples were analyzed by using the newly developed and validated HPLC methods. SPE was used by modification of the mobile phase and washing solvents in different ratios to achieve better accuracy, precision, linearity, earlier retention times, clear elution and recovery. The study showed that ceftazidime and cefepime were stable for up to 16 hours while cefotaxime was stable for up to 24 hours in all TNAs formulations and there after degraded more than 10% respectively. Physico-chemical compatibility results showed that there were no significant changes in pH, globules size, zeta potential and concentrations of sodium and potassium in all of the formulations (all $p \geq 0.05$). In addition, there was no precipitation or flocculation observed in any of the formulation. The newly developed HPLC methods were able to detect selected cephalosporins more accurately, precisely, effectively and efficiently. In conclusion, this study showed that ceftazidime and cefepime were compatible and stable for 16 hours in/with TNAs while cefotaxime was compatible and stable for 24 hours in/with TNAs.

CHAPTER ONE

GENERAL INTRODUCTION

1.1. Introduction

Parenteral nutrition (PN) or total parenteral nutrition (TPN) is an intravenous administration of amino acids, glucose, lipids, electrolytes, vitamins and trace elements (Nelson *et al.,* 1986). In individuals who are unable to tolerate food by oral or enteral route, total parenteral nutrition is the best alternative route to sustain their lives. PN is often needed as an adjunct in cancer therapy and in many particular situations, i.e. when a patient is unable to take adequate oral calories for more than a week, or has poor absorptive capacity after surgery, or has a fistula, acute hepatic or renal failure, or an inflammatory bowel disease (Siow, 2008). Parenteral nutrition is also a standard practice for providing exogenous nutrients to the patients having several diseases in order to improve their nutritional status and to avoid any catheter related infection (Alfieri *et al.,* 1998). Composition of PN admixtures primarily depends on the individual needs of nutrients and electrolytes. The decision to start PN therapy and the choice of the PN admixtures should be tailored to the patient's diagnosis and nutritional status to avoid over or under nutrition (Iacobelli *et al.,* 2010; Leung, 1995; Vanek *et al.,* 1997; Verma *et al.,* 2010; Weiler *et al.,* 2006).

PN for children is different from adults because it contains relatively more electrolytes and other nutrients (Iacobelli *et al.,* 2010). Prime goals of nutritional support during first few days of postnatal life are, to maintain the liquid balance, to normalize glycemia and to maintain levels of electrolytes and minerals in the body. In general, the liquid needs of large immature neonates vary from 90 to 140 mL/kg/day when they are in radiant warmers while 80 to 120 ml/kg/day when they are in incubators. Liquids are normally administered to immature neonates as 5% or

7.5% solutions of glucose, to avoid glycemic disorders which are common in the first days of life (Diekmann *et al.,* 2005; Falk, 1998; Jadhav *et al.,* 2007; Pauls *et al.,* 1998; Ronchera-Oms *et al.,* 1995). Nowadays, it is desirable to supply PN admixtures' components in a single bag called All-in-One Total Parenteral Nutrition Admixtures (AIO TPN Admixtures) or Total Nutrient Admixtures (TNAs).

TNAs have become an extensively used therapeutic tool to treat malnourished patients receiving parenteral nutrition after the approval of admixing intravenous fat emulsions with dextrose solutions and various amino acids. The advantages of TNAs include decreased administration costs compared with the conventional piggyback method for infusion of intravenous fat emulsions into parenteral nutrient solutions and increased tolerance of intravenous fat emulsions in neonates when the fat is infused over a period of 24 hours. Microbial growth studies have also demonstrated a reduction in microbial growth in the TNAs when compared with intravenous fat emulsions alone infused over 24 hours (Driscoll *et al.,* 2000; Driscoll *et al.,* 2007; Eskew, 1987; Gilbert *et al.,* 1986; Simmons *et al.,* 1982).

Advantages of TNAs are, number of nurse handlings is lowered, the risk of thrombophlebitis is reduced, therapeutic errors are minor and all nutrients are supplied continuously over the day. TNAs are complex nutrients solutions containing lipid emulsions, which need sterility, stability and free from precipitates. In TNAs numerous components (amino acids, carbohydrates, lipids, water for injection, electrolytes, trace elements and vitamins) interact according to different reactions which are fairly less known to date. There are many factors like biphasic characteristic of lipid emulsion which can affect the compatibility of TNAs and can cause physicochemical

instability of TNAs. Thus a careful quality control during compounding as well as in clinical practice is vital. In contrast to TNAs for adults, hardly there is any information available about the stability of neonatal TNAs which contain more nutrients (Hardin, 1993; Imrie *et al.,* 2002; Lorenz, 2008; Porcelli and Sisk, 2002; Rigo and Senterre, 2006).

The limitations of the TNAs are related to the lack of information regarding stability when different amino acids are used or varying concentrations of electrolytes or other additives are admixed with the emulsion system. The predominant factors affecting emulsion particle size, or stability are pH and increased electrolyte concentration. The significance of emulsion globule size has been established by reports of adverse reactions associated with the infusion of particles greater than 6 μm in size (Driscoll *et al.,* 2007). As pH varies with different crystalline amino acid formulations and concentrations, the stability of each amino acid product must be tested with a given intravenous fat emulsion in various concentrations. For better clinical significance, various concentrations of electrolytes and minerals are added to the TNAs to make them more appropriate for individual patients (Bullock *et al.,* 1992, D'Angio *et al.,* 1987; Driscoll *et al.,* 2007; Harrie *et al.,* 1986; Lee *et al.,* 2003; Mershon *et al.,* 1986; Sayeed *et al.,* 1986; Simmons *et al.,* 1982).

Although the improvement of multi compartment bags has amplified the shelf-life of TNAs but TNA therapy is still having several metabolic risks, infections and mechanical complications. In addition, the physicochemical instability and risks of substrate precipitation may make TNAs more obscure. Parts of these complications can be avoided by stern pharmaceutical procedures and clinical guidelines. It is also very important that all TNAs formulas/ratios should be prepared

according to strict pre-established procedures which can reinforce quality control principles and guidelines (Batani *et al.,* 2007; Dudrick, 2009, Maisonneuve *et al.,* 2004; Menne *et al.,* 2008).

The addition of medications and other additives to TNAs has become common practice in order to reduce intravenous catheter manipulations and minimizing the risk of contamination (Atkinson, 2001; Franasois *et al.,* 1997; McGuire *et al.,* 2004). Therefore addition of antibiotics to TNAs before the start of the infusions would be preferable in order to lessen various infections which may often cause problems particularly in very small newborns that have immature immune systems and reduced muscle mass. Moreover, by adding antibiotics to the fluids, which are infused via a pump, it is quite possible to maintain a higher steady-state concentration than the minimal inhibitory concentration for most bacterial strains. As an example amino glycosides administered in this pattern have shown a high cure rate in adults as well as in neonates (Bodey *et al.,* 1995; Pierre *et al.,* 2009).

Addition of antimicrobials and antibiotics to the TNAs to treat central catheter-related infections has shown a number of practical advantages like (i) the TNAs containing antimicrobials can be given during home nutrition therapy (ii) manipulations involving the catheter are not needed to administer the antimicrobials/antibiotics hence there is less risk of infections and less need of nursing staff (iii) there is no need for additional fluids to dilute the antimicrobials or antibiotics, which can be very useful in neonates and infants having fluid restrictions (Forbes, 2004; Tounian *et al.,* 1999).

Addition of antibiotics to the TNAs often raises question of stability of the antibiotics over longer periods e.g. 24 hours. Stability of antibiotics in/with TNAs containing electrolytes, carbohydrates and protein solutions has been examined rather comprehensively, whereas the stability and compatibility of antibiotics in combination or alone in synthetic amino acid solutions, carbohydrates together with fats has only been studied by one or two groups (Anthony and Rubin, 1999; Stein, 1999; Wyatt *et al.,* 1972). Unfortunately, nearly all stability studies of drugs in pediatric nutrient solutions focus on drug concentrations/availability but not on nutrient stability. Above all, data about micronutrient stability after adding medication to pediatric TNAs is almost rare in the literature which is vital for the welfare of the patients especially neonates and infants. Various issues may be related to micronutrients and macronutrients' physical and chemical instability in TNAs together with medications (Forbes, 2004; Hardin, 1993; Leung *et al.,* 1995).

Stability testing of pharmaceuticals is essential for three reasons. First, patient safety by assuring that patient receives a uniform dose of a drug throughout the shelf life of formulation. Second, to meet legal requirements concerning with identity, strength, purity and quality of a drug. Third, to control economic repercussions involved in developing and marketing unstable products. Currently, around the globe, it is a common practice to administer different antibiotics especially cephalosporins in/with PN admixtures in order to treat various infections or diseases. Thus it is very important to check their stability in/with these TNAs in order to administer a precise dose and to assure that patients will receive a uniform dose throughout the shelf life of formulations. To date there is no sufficient literature available that can confidently describe the stability of some commonly used antibiotics like cephalosporins in/with PN admixtures. This project is

especially aimed to check the stability and compatibility of commonly used antibiotics (ceftazidime, cefotaxime and cefepime) in/with TNAs.

1.2. Literature review

1.2.1. Parenteral nutrition (PN)

The standard use of parenteral nutrition (PN) in clinical practice started in 1968, after Dudrick *et al.,* efforts. These pioneers explained that parenteral therapy of amino acids and glucose concentrated solutions together with minerals, vitamins and micronutrients may result in more growth in children and adults. Initially PN admixtures were administered mostly with amino acids and glucose. Now, parenteral nutrition (PN) includes intravenous administration of amino acids, glucose, lipids, electrolytes, vitamins and trace elements (Dudrick, 2009, Waitzberg *et al.,* 2006).

Parenteral nutrition (PN) can be divided into:

- Total parenteral nutrition (TPN), where all nutrient needs are covered by intravenous way without any significant enteral intake.
- Supplementary parenteral nutrition, where a patient receives some part of his/her food via gastrointestinal tract and the rest is infused parenterally (Pertkiewicz *et al.,* 2009).

TPN admixtures are usually referred to as Two-in-One (TIO) or All in- One (AIO) where these refer to admixtures that are either

- TIO an aqueous formulation (mixture of dextrose and amino acids free of fat)

- ❖ AIO infusion which will usually contain all the required PN components, including lipid in the form of an emulsion (Barnett *et al.,* 2009).

Nowadays, it is desirable to supply PN from one compartment which is called AIO TPN admixtures (All-in-One Total Parenteral Nutrition Admixtures) or TNAs (Total Nutrient Admixtures). In this system, all of the individual components (sterile injections or infusions) are admixed into a single sterile plastic container, providing the user with a complex pharmaceutical formulation in the form of a single easy to use infusion system. Advantages of this system are, the number of nurse handlings is lowered, the risk of thrombophlebitis and errors is reduced and all nutrients are supplied incessantly over the day (Barnett *et al.,* 2009, Dudrick, 2009).

TNAs are sterile large volume parenteral infusions aseptically prepared from required nutritional components (e.g. amino acids, glucose, lipid, electrolytes, trace elements and vitamins). Parenteral nutrition (PN) is also an alternative way for patients who cannot eat food or cannot meet their caloric needs totally or partially via gastrointestinal route (Gunsar *et al.,* 2010). In all, there may be more than 39 individual additives, each of which has its own physicochemical characteristics (Kearney *et al.,* 1998).

At the moment in various countries, preparation of TNAs is extensively practiced by their hospital pharmacy departments. The foremost objective is to integrate all of the nutritional necessities into one infusion bag for administration to the patients on daily basis. TNAs can be given long shelf lives i.e. in weeks or in months, depending upon the specific formulation (Kearney *et al.,* 1998). Undeniably TNA is a leading development in medical therapy for the

provision of energy and other essential nutrients to the seriously ill patients who are unable to eat. TNAs feeding significantly reduce both morbidity and mortality in seriously ill medical or surgical patients. However, PN feeding often augments the risk of infectious complications compared with enteral nutrition (Ling *et al.,* 2010).

Children treated with chemotherapy have a suppressed immune system and are very susceptible to infections. It is important to lessen the risk of infections for these patients due to intravenous administrations. TNA for children is different from that of adults, because it contains relatively more electrolytes or other components. On contrary to TNA for adults, there is very less information about the stability of lipids in neonatal TNAs, prepared and administered from one compartment (all-in-one). The composition of the TNAs normally depends on the body mass and on the phase in the nutrition period. Thus, it should be adapted to individual needs of nutrients and electrolytes (Barnett *et al.,* 2009; Koorenhof and Timmer, 1992; Lemons *et al.*, 2001).

1.2.2. Parenteral nutrition in neonates and infants

Parenteral nutrition is a lifesaving medical intervention for many pediatric patients. Parenteral nutrition provides energy for growth and tissue repair when the gastrointestinal tract cannot be used due to small stomach capacity, immature gastrointestinal tract and illnesses. This is especially true for preterm or low birth weight neonates who represent the highest percentage of the pediatric population requiring parenteral nutrition. A small premature infant whose nutrition reserve are limited can survive 4-5 days if fed water alone and 11 days if provided with 10% dextrose alone (Brine and Ernst, 2004; Hack and Fanaroff, 2000; Oden and Bourgeois, 2000). In more recent years, the earlier introduction and more aggressive advancement of PN was shown

to be safe and effective, even in the smallest and most immature infants (Thureen and Hay, 2001).

The neonatal period is a vital interval where nutrition can influence the infant's growth and development. Failure to provide essential nutrients can result in serious conditions, including growth retardation, reduced respiratory and cardiac reserve, impaired immune system, impaired tissue and muscle functions and neurological deficits (Sedlacek *et al.,* 2006; Wilson *et al.,* 1997). The period of 30 weeks of gestational age to 6 months of life is vital for brain development while nutrition compromised in this period may cause everlasting loss of brain development. Therefore, the nutrient support of the preterm and critically ill infant is extremely important, not only for rapid endurance but also for a long-term outcome (Chaudhari and Kadam, 2006, Mermel *et al.,* 2001).

It is very difficult to survive for many critically ill preterm infants in their first weeks of life because of the infant's small stomach capacity and immature gastrointestinal tract. In such cases parenteral nutrition becomes essential for nutrition support; either as a supplement to enteral feedings or as the total source of nutrition (Allwood *et al.,* 1996; Driscoll, 1996; Uuml *et al.,* 2009). According to ASPEN and ESPEN clinical guidelines, PN in neonates is recommended in various diseases i.e. gastrointestinal diseases like significant anomalies of the gastrointestinal tract requiring surgery, chronic intractable diarrhea, vomiting, inflammatory bowel disease, radiation enteritis, chronic intestinal obstruction or pseudo-obstruction, mucositis, esophageal stricture, tracheoesophageal fistula, severe malabsorption, fistula, congenital microvillous atrophy, diseases of other organs like hepatic coma, pancreatitis, renal failure, congenital heart

disease, severe respiratory disease, various surgical conditions (other than gastrointestinal tract) like preoperative support, postoperative support, severe burn and trauma, numerous psychiatric disorders like anorexia nervosa, neoplasia and the patients with mal enteral nutrition (Allwood *et al.,* 1996; Driscoll, 1996; Koletzko *et al.,* 2005; Lee, 1996; Mehta *et al.,* 2009; Uuml *et al.,* 2009).

1.2.3. Parenteral nutrition in Malaysia

Firstly parenteral nutrition services in Malaysia were introduced in 1986 at two hospitals, Hospital USM Kelantan and Hospital Pulau Pinang. Since then, there are numerous reported studies on PN practice in Malaysian hospitals presented in various local and international seminars and conferences (Batani *et al.,* 2007).

1.2.4. Components of TNAs

The proportions and mix of components of TNAs used for intravenous nutrition can vary considerably depending upon the patient's nutritional status and underlying medical or surgical conditions. The components available for TNAs are macronutrients and micronutrients and are detailed below (Cooke and Griffin, 2009; Ehrenkranz *et al.,* 2006; Rigo *et al.,* 2001).

1.2.4 (a). Macronutrients

Macronutrients constitute the majority of an individual's diet, "thereby supplying energy, and the essential nutrients that are needed for growth, maintenance, and activity". Macronutrients include carbohydrates, proteins and fats. Carbohydrates, proteins, and fats are interchangeable as sources

of energy, with fats yielding 9 calories per gram, and protein and carbohydrates each yielding 4 calories per gram (Slicker and Vermilyea, 2009).

(i). Amino acids

Amino acids prevent catabolism. Rapid administration of amino acids through TNA therapy attains earlier positive nitrogen balance in neonates and infants. It also dwindle the rate and severity of neonatal hyper glycaemia by enhancing endogenous insulin secretion and augmenting growth by enhancing the secretion of insulin and insulin-like growth factors (Colomb *et al.,* 2002, Denne, 2001; Ehrenkranz, 2007; Embleton *et al.,* 2001). Protein are generally started at 1g/kg/day in the form of crystalline amino acids up till 3rd to 4th post-natal day, afterwards it is increased to 3.0 g/kg/day in terms and 3.7 to 4.0 g/kg/day in the extremely low birth weight (ELBW) infants. Amino acids provide 4 kcal/g when oxidized for energy (Heiman and Schanler, 2007; Khanna and Gopalan, 2007; Liusuwan *et al.,* 2005; Saitoh *et al.,* 2001; Shulman and Phillips, 2003; Valentine and Puthoff, 2007; Van Goudoever *et al.,* 1995).

Essential amino acids cannot be synthesized by the human body and are required to maintain and promote cell growth. All the commercially available solutions contain eight essential amino acids in varying proportions. Eminent essential amino acids are aspartate, glutamate, taurine, and tyrosine. Cysteine is also considered as conditionally essential in premature infants due to a theoretical insufficiency of enzymatic activity for the conversion of methionine to cysteine (Ganger and Craig, 1990; Heird and Gomez, 1996). Non-essential amino acids are those amino acids which can usually be produced by human body. These amino acids are used to increase the amount of nitrogen available from the solutions and the optimum ratio of essential to non-

essential amino acids has yet to be agreed between workers. The nonessential amino acids are available as metabolites of other amino acids or precursors via enzymatic degradation (Camelo and Jorge, 1995). The semi- can be added in the TNAs if body does not synthesize them due to the patient's age or a disease state (Helms *et al.,* 1999).

(ii). Glucose

Carbohydrate is delivered in 2.5 to 70% dextrose solutions that provide 3.4 kcal/g. Glucose is also called dextrose. Dextrose is the primary source of parenteral carbohydrate. Dextrose is needed by the central nervous system, white blood cells, red blood cells, and renal medulla. Each gram of hydrated dextrose used in parenteral nutrition yields 3.4 kcal. There is a relatively high energy requirement in the Extremely Low Birth Weight (ELBW) infants. In these neonates large and continuous source of glucose is required because of comparatively large body proportion of metabolically active organs i.e. liver, spleen, kidney and brain (Bolder *et al.,* 2009, Valero *et al.,* 2001). In the ELBW the minimum Glucose Infusion Rate (GIR) is 6 mg/kg/min to maintain adequate energy for the brain and an additional 2-3 mg/kg/min of glucose per gram of protein intake is necessary to support protein deposition (Corridan *et al.,* 2001). The maximum rate is 12 to 13 mg/kg/min However, lower is applied if lipid is administered concurrently but in practice glucose administration is often limited by development of hyperglycaemia which is reported in 20-80% of ELBW infants (Lloyd, 1998). Strategies for the management of hyperglycaemia in the ELBW include decreasing glucose administration, administering intravenous amino acids (which increase insulin secretion) and infusing exogenous insulin infusions (Bolder *et al.,* 2009; Burrin *et al.*, 2003; Corridan *et al.,* 2001; Frankfort *et al.,* 1993; Jones *et al.,* 1993; Lloyd, 1998; Valero *et al.,* 2001).

(iii). Fatty Acids

Fat is needed to prevent essential fatty acid deficiency, serve as energy substrate and improve delivery of fat soluble vitamins. LBW infants may have undeveloped systems for fat metabolism. A number of clinical conditions inhibit lipid clearance e.g. infection, stress and malnutrition. Lipid is generally started at 1g/kg/day and steadily increased to a limit of 3 g/kg/day (sometimes up to 3.5g/kg/day in the ELBW). It is infused continuously over as much of the 24 hour period as practical and smaller doses are used in patients with infection, compromised pulmonary function or hyper bilirubinemia (Behrman *et al.,* 1976; Chauhan *et al.,* 2008; Herrera, 2002; Koletzko *et al.,* 2005; Lima, 1989; Lima *et al.*, 1988; Lopez-Herce *et al.,* 2008; Takahashi and Sawaguchi, 1983).

Fat is administered as lipid emulsions of neutral triglycerides, primarily polyunsaturated fatty acids (PUFA) that are vital for normal growth and development, retinal development and function, brain development, and cell structure and function (Ehrenkranz *et al.,* 2006). Intravenous lipid plays two separate roles in PN therapy. One is as a source of essential fatty acids as well as long chain polyunsaturated fatty acids. The other function of intravenous lipid is as energy substrate. Lipid emulsion has benefits over concentrated glucose solutions because of their isotonicity and greater energy density, the later meaning that less volume is required per calorie (Ehrenkranz, 2007; Gramlich *et al.,* 2004; Hay, 2008; Jadhav *et al.,* 2007; Jr. Martinez, 2005; Shulman, 2000; Smolkin *et al.*, 2010; Steward and Pridham, 2002).

1.2.4 (b). Micronutrients

Micronutrients are vitamins, electrolytes and trace minerals/elements. Vitamins and trace minerals are labeled as micronutrients because the body only requires them in very small amounts. Vitamins are organic substances that we ingest with our foods, and that "act as catalysts, substances that help to trigger other reactions in the body". Trace minerals are inorganic substances that once ingested play a role in a "variety of metabolic processes, and contribute to the synthesis of such elements as glycogen, protein, and fats" (Slicker and Vermilyea, 2009).

(i). Vitamins

Infants on long-term PN therapy will generally require some vitamin supplementation. Vitamins are essential components of PN because they are necessary for normal metabolism and cellular function of the body. The American Society for Clinical Nutrition (ASCN) has established guideline which is shown in Table 1.1 (Greene *et al.,* 1988). The vitamins which normally added into PN are: Vitamin A (Retinol), B1 (Thiamines), B2 (Riboflavine), B6 (Pyridoxine), B12 (Cyanocobalamin), B (Nicotinamide), B (Biotin), B (Pantothenic acid), B (Folic acid), C (Ascorbic acid), D (Calciferol), E (Tocopherol) and vitamin K (Phytomenadione) (Lang, 1989; Porcelli *et al.,* 2004; Van der Horst *et al.,* 1989).

(ii). Electrolytes

Electrolytes in maintenance or therapeutic doses need to be added every day to the parenteral nutrition solution to preserve electrolyte homeostasis. Each patient's requirements for individual electrolytes depend on the primary disease state, renal and hepatic functions, pharmacotherapy,

past intake, renal or extra renal losses, and nutritional status. Losses of extra renal electrolytes may be due to different diseases like diarrhea, vomiting, fistulas, or nasogastric suctioning. Dosage of every electrolyte should be made on patient needs (Biesalski *et al.,* 2009; Hay, 2005; Schmidt, 2000).

Potassium, sodium, and chloride are vital to human life and their needs are reliant on requisite losses and abnormal losses. Predictable and prudent intakes are entirely depended on accrual needs and fecal and urinary losses. Sodium and potassium can be given as chloride, lactate, or phosphate salts. Calcium, phosphorus, and magnesium are the most copious minerals in the body. They are closely interrelated to each other in metabolism, the formation of tissue structure, and function. Calcium and phosphorus needs may be greater in the neonate due to rapid skeletal bone development. The sufficiency of these valuable nutrients from PN admixtures has been widely studied in the premature population (Koo *et al.,* 2000; Loui *et al.,* 2002; Pelegano *et al.,* 1989; Schanler and Rifka 1994; Sievers *et al.,* 2000; So and Ng, 2005; Vilelsis, 1987).

(iii). Trace elements/minerals

Trace elements are Zinc, Copper, Selenium, Chromium, Iron, Manganese, Cobalt, and Molybdenum. Trace elements are critical micronutrients that are metabolic cofactors and are vital for the appropriate functioning of numerous enzymatic pathways in neonates. Parenteral guidelines for molybdenum and iodine have not been established; however, these trace elements are available commercially (Pluhator-Murton *et al.,* 1999; Van der Horst *et al.,* 1989). The suggested amounts of zinc, copper, manganese, and chromium for neonates and infants are listed in Table 1.1.

Table 1.1. Daily requirement of nutrients in TNAs for neonates and infants (adapted from Brine E and Ernst J (2004), *Newborn and Infant Nursing Reviews,* 4, 133-155.)

Nutrient Additive	Usual Daily Requirements in TPN	
Neonatal amino acid	For maintenance: 1.5-2.5 g/kg/d For ELBW infants, begin at a minimum of 1.5 g/kg/d as soon as possible.	Goals for growth: 3.5 g/kg/d for <1,000 grams 3.0 g/kg/d for 1,000-2,500 grams 2.5 g/kg/d for >2,500 g 4.0 g/kg/d for some infants with greater needs
Cysteine hydrochloride	40 mg/g of amino acids (120 mg/kg maximum) Refer to acetate guidelines for ELBW infants (see below under Excess anions)	
Dextrose	For maintenance: 4-6 mg/kg/min (endogenous hepatic glucose production) 8-10 mg/kg/min (preserves carbohydrate stores)[10]	Goals for growth: 12-13 mg/kg/min Usual maximum concentration: 12.5% peripheral route 20-25% central route
Lipid (20% emulsion from 100% soy oil)	0.5-4.0 g/kg/d; Begin 0.5-1.0 g/kg/d and advance by 0.5-1.0 g/kg/d Essential fatty acids met with 1.0 g/kg/d and at least 80 kcal/kg/d Delivered as a component to the amino acid–glucose solution (admixture) or as a separate solution	
Energy	Goals for maintenance Preterm/term: 60 kcal/kg/d	Goals for growth Preterm: 90-110 kcal/kg/d Term: 80-90 kcal/kg/d Dextrose (40-60%), lipid (40-50%), protein (10-15%)
Carnitine	2-10 mg/kg/d not to exceed 50 mg/kg/d[106]	
Heparin	1 unit/mL not to exceed 137 units/d 0.5 unit/mL for ELBW infants when volume exceeds 150 mL/kg/d	
Sodium (Na) as chloride or phosphate	2-4 mEq/kg/d	Positive nitrogen balance is critical for growth; ELBW infants may require increased intake
Potassium (K) as chloride or phosphate	2-4 mEq/kg/d	Consider omitting in ELBW infants until renal sufficiency is well established
Chloride (Cl)	2-4 mEq/kg/d	Usual Na:Cl is 1:1
Excess anions Acetate Chloride	Excess anion equivalent = (Na + K) − (Cl + P) Usually provide electrolytes as acetate Always use acetate if adding cysteine hydrochloride for ELBW	
Calcium (Ca) as gluconate	1-3 mEq/kg/d for maintenance	3-4.5 mEq/kg/d for growth (see text for solubility limits) Should be administered through a central line rather than a peripheral line in premature infants
Phosphorus (P) as sodium or potassium phosphate	1.3 mmol/kg/d for maintenance[17]	1.5-2.0 mmol/kg/d for growth
Magnesium (Mg)	0.25-1.0 mEq/kg/d Begin ELBW infants at low end	Increased needs for infants with ostomy losses

Continued

Nutrient Additive	Usual Daily Requirements in TPN
Vitamins as MVI-Pediatric	Premature: 2 ml/kg/day to a maximum of 5 mL/d Term: 5 mL/d
Zinc (Zn) as sulfate or in pediatric trace element (PTE) solution	400 μg/kg/d: Preterm infants and all infants with gastrointestinal losses 250 μg/kg/d: Term infants 0-3 months 100 μg/kg/d: Term infants > 3 months and all infants with long-term TPN
Copper (as sulfate or in PTE)	Withhold during the first 2 weeks of TPN, then initiate at 20 μg/kg/day Decrease amount or withhold with complication of obstructive jaundice
Selenium in PTE	Withhold during the first 2 weeks of TPN Decrease amount or withhold with complication of renal dysfunction Premature: Begin at 1.3 μg/kg/d and advance to 1.5-2.0 μg/kg/d Term: 2.0 μg/kg/d
Chromium in PTE	Withhold during the first 2 weeks of TPN Decrease amount or withhold with complication of renal dysfunction Premature: Begin at 0.05 μg/kg/d and advance to 0.05-0.2 μg/kg/d Term: 0.2 μg/kg/d
Manganese in PTE	Withhold during the first 2 weeks of TPN Decrease amount or withhold with complication of obstructive jaundice Premature: Begin at 0.75 μg/kg/d and advance to 1.0 μg/kg/d Term: 1.0 μg/kg/d
Iodide (I)	Withhold for the first 3 months of TPN Premature: 1.0 μg/kg/d
Molybdenum (Mb)	Withhold for the first 3 months of TPN Decrease amount or withhold with complication of renal dysfunction Premature/term: 0.25 μg/d
Iron (Fe) as dextran or ferrous citrate	May withhold until 2 months of age (Premature), 3 months of age (Term) and considered for infants who do not receive regular blood transfusions. Premature/Term: 1.0-2.0 μg/kg/d
Fluoride (Fl)	Withhold for the first 3 months of TPN then provide premature with 500 μg/kg/d Solutions may be contaminated with fluoride

Zinc is unanimously suggested from day one of PN therapy, while the rest trace minerals are commonly administered after three, five, or twelve weeks of PN without any significant enteral feeding (Hardy *et al.,* 2001). Zinc requirements are increased in metabolic stress secondary to increased urinary losses and in gastrointestinal disease secondary to ostomy or diarrheal losses. ELBW infants need additional zinc than term infants (Pluhator-Murton *et al.,* 1999). Selenium stores have been revealed to be depleted in patients receiving long-term parenteral nutrition or in those with thermal injury, acquired immunodeficiency syndrome, or liver failure. Therefore,

selenium should be added initially to the parenteral nutrition solution for patients with these disease states or conditions (Dworkin, 1994; Hardy *et al.,* 2001; Hunt *et al.,* 1984; Pluhator-Murton *et al.,* 1999). Recommended intravenous intake of trace elements for neonates and infants has been shown in Table 1.1.

Parenteral iron supplementation may be delayed until two months of age in premature infants and three months of age in term infants but it can be considered for those infants who do not receive regular blood transfusions. Supplementation of iodide in TNAs may not be necessary because iodide needs may be met by other routine usages of topical iodide-containing disinfectants, detergents and other environmental sources (Al-Saleh *et al.,* 2005; Baptista *et al.,* 1984; Blazewicz *et al.,* 2010; Ekin *et al.,* 2003; Leung, 1995; Leung, 1998; Leung *et al.,* 1995; Ono *et al.,* 1995; Papageorgiou *et al.,* 2002; Rahman *et al.,* 2009; Yanik *et al.,* 2004).

1.2.5. Antibiotics in neonates and infants

In neonates, most common early-onset bacterial infections are caused by group B streptococci, enterococci, Enterobacteriaceae and *Listeria monocytogenes*. Coagulase-negative staphylococci, particularly *Staphylococcus epidermidis* are the main pathogens in late-onset (nosocomial) infections, especially in high-risk patients such as those with low birth weight, umbilical or central venous catheters or undergoing prolonged ventilation (Pacifici, 2011; Fanos and Agnola, 1999). The primary objective of the pediatricians is to identity all potential cases of bacterial infections quickly and begin empirical antibacterial treatment immediately while waiting for the results of cultures and sensitivity tests. Combination therapy is often recommended for initial empirical treatment in children (McCracken, 1985; Fanos and Agnola, 1999). In early-onset

infections, an effective first-line empirical therapy is ampicillin plus a third-generation cephalosporin such as cefotaxime or ceftazidime. Combination therapy is particularly useful in neonatal meningitis (mean duration of treatment 14 to 21 days) and in patients at risk of nephrotoxicity (Fanos and Agnola, 1999).

Neonatal sepsis is another life-threatening emergency and any delay in treatment may cause death. Initial signs of neonatal sepsis are slight and nonspecific (George, 1985; Yurdakök, 1998). Initial empirical antibiotic therapy for infants who developed sepsis, must cover the organisms associated with early-onset sepsis as well as hospital-acquired pathogens such as staphylococci, enterococci and *Pseudomonas aeruginosa* (Downie *et al.,* 2012; Yurdakök, 1998). In cases showing increased risk of staphylococcal infections (e.g. presence of vascular catheter), Pseudomonas infections (e.g. presence of typical skin lesions), anti-staphylococcal or anti-Pseudomonas agents may be preferred as an initial empirical therapy. In these situations, third-generation cephalosporins alone or in combinations with penicillin or ampicillin have been used where they gave superior results (McCracken, 1985; Downie *et al.,* 2012).

1.2.6. Cephalosporins in neonates and infants

Cephalosporins are appropriate alternatives when other commonly used antibiotics are not available. They have few potential advantages that make them distinguished from other antibiotics to treat various infections in children. Cephalosporins are more resistant to beta-lactamases and are easy to administer and monitor as compared to penicillins (Cotton *et al.,* 2006; Bluestone *et al.,* 2003). Cephalosporins have a wide margin of safety and are unlikely to

cause toxic signs even in overdose. Cephalosporins are drugs of choice against Pneumonia and urinary tract infections caused by Klebsiella. Cephalosporins also widely use in other infections like otitis media, acute sinusitis, pharyngitis, tonsillitis, lower respiratory tract infections and skin infections. In children cephalosporins are used for skin infections and acute bacterial otitis media (Bluestone *et al.,* 2003).

In this study we selected cephalosporins as in infants and neonates they are widely used group of antibiotics with a beta-lactam ring, resistant to beta-lactamases, and cover broad spectrum of gram-positive and gram-negative bacteria. Although all cephalosporins are potent but there are few infectious diseases in children where these drugs offer a unique advantage over other available antimicrobial agents (Charles *et al.,* 2003; Cotton *et al.,* 2006). Cephalosporins are also commonly prescribed either orally or parenterally for the treatment of numerous infections because of their wide safety margin compared with penicillins. Skin testing with a parent cephalosporin antibiotic is not necessarily required as compare to penicillins (Baek-Nam *et al.,* 2010). Penicillins are the antibiotics that most commonly induce severe or life-threatening IgE-mediated reactions (anaphylaxis). Third-generation cephalosporins are generally well tolerated in neonates. When antibacterials are used in neonates, accurate determination of dosage is required, particularly for compounds with a low therapeutic index and in patients with renal failure (Fanos and Agnola, 1999).

In few settings, third-generation cephalosporins are also combined with an aminoglycoside in places where aminoglycoside-resistance is high. Among the third-generation cephalosporins,

cefotaxime and ceftazidime possess wider anti-Pseudomonas activities (Yurdakök, 1998). Cefoperazone, cefotaxime and ceftazidime are parenteral products with efficacy in vitro against gram-positive cocci and gram-negative bacilli. Ceftazidime was first introduced for clinical use in the United States in 1985. This drug has excellent activity and often used in middle-ear infections in children and infants. Ceftazidime is drug of choice in surgical prophylaxis as well (Murki *et al.,* 2010; Charles *et al.,* 2003). Ceftazidime is first line of choice to treat *Pseudomonas aeruginosa.* Serious and life threatening infections like bacterial endocarditis are well treated by cephalosporins than other antibiotics. Cefuroxime and cefepime are widely utilized for the treatment of bronchitis, UTI's, community acquired pneumonia (Bluestone *et al.,* 2003). Ceftriaxone and cefotaxime are drugs of choice in neonatal/childhood meningitis caused by *Haemophilus influenzae.* Cefepime is a fourth generation parenteral cephalosporin with excellent activity against gram-positive organisms and enhanced gram-negative activity including *Pseudomonas aeruginosa* (Capparelli *et al.,* 2005; Charles *et al.,* 2003).

1.2.7. Administration of drugs in/with TNAs and parenteral nutrition

In TPN therapy drugs are administered by three different methods i.e. Piggyback technique, using multiple lumen catheters and admixing drugs into volumetric chambers of IV fluids (Trissel *et al.,* 1999). In IV Piggyback (abbreviated as IVPB) technique, a second IV medication or fluid is hung alongside the first fluid/drip and is attached to the first set of IV tubing through one of the injection ports that is below the drip chamber of the primary IV tube. These both fluids lines are connected by means of Y-site connectors (Russell *et al.,* 2007). During simultaneous Y-site administration of two infusions, contact does not occur until they reach the common Y-site. Contact times of the admixtures from that point through the remainder of the

tubing until they reach the patient's bloodstream are typically 15 to 30 minutes but can go up to 60 minutes or beyond in slow administration situations (Trissel *et al.,* 1999). Second method where multiple lumen venous catheters are used is also expensive and risks of catheter-related bloodstream infection are more compared with single-lumen catheters (Zürcher *et al.,* 2004).

Sometimes separate administration of the drugs is not preferred because volume to be administered is more than 3 mL or it is advisable to give the medication over an extended period of time. In this case, we can simply inject the medication into one of the injection ports (volumetric chambers) on an IV line (Zürcher *et al*., 2004). Separate administration is not always possible and the line being used to infuse TPN continuously may be the only intravenous access available. Admixing of the drugs into volumetric chambers is cost effective, convenient and time saving but can only be possible if compatibility and stability of the admixing drugs with TPN admixtures is evident (Tanmoy and Ghosh, 2011). In this technique contact time of drug and TPN fluids is longer than Piggyback. In this method, desired drug is added into volumetric chamber by opening the sliding clamp. For drug addition, first disinfect the rubber injection port of the volumetric chamber and then incorporate drug by mixing gently. Regulate the flow rate of IV infusion accordingly and then close the clamp of the volumetric chamber (Russell *et al.,* 2007; Trissel *et al.,* 1999; Zhang *et al.,* 2000).

Aggressive and early antimicrobial therapy with broad-spectrum antibiotics may be helpful in keeping the mortality rate low. It is preferable to start antimicrobial therapy with PN infusions for critical patients to avoid excessive catheter infections, which are difficult to treat and can potentially invite the risk of other complications (Puzovic and Hardy, 2007). Antibiotics with PN

therapy are also used to treat severe nosocomial or general infections either in adults or in children (Zaccardelli *et al.,* 1990). Directives of the Joint Cornmission on Accreditation of Hospitals, USA in 1999 suggest that medication for intravenous use should be added to solutions in central pharmacies of the hospitals (Buchman, 2001).

Addition of drugs to parenteral nutrition is always a potential source of instability. When a drug is added PN admixtures, the contact time between the drug as well as the excipients and nutritional components present in the formulation can be affected (Buchman, 2001). Because of the very complex physico-chemical composition of the PN admixtures, a long contact time represents a higher risk for drug nutrient interactions to develop (Zaccardelli *et al.,* 1990). Turbidity, visual inspection, time, temperature and pH changes are standard assessments which should be done before administration into body. High performance liquid chromatography (HPLC), lipid particle counting and globule sizing are sophisticated electronic techniques which are normally used to investigate incompatibility, instability or different sorts of drug interactions (Puzovic and Hardy, 2007).

The addition of drugs to PN admixtures or their co-administration requires thorough knowledge of the stability of drugs within these complex solutions (Puzovic and Hardy, 2007). Antibiotic stability has been assessed in relatively few publications, and in most of these, stability and compatibility studies have been limited to mixtures of the antibiotics with normal saline or 5% dextrose (Pluhator-Murton *et al.,* 1999). In past, amino acid solutions of varying composition in combination with vitamins, minerals, glucose, and electrolytes have been utilized in intravenous infusions (Buchman, 2001). Relatively fewer information on the stability and compatibility of

drugs in intravenous PN admixtures is available in product information booklets, package leaflets and in the published scientific literature (Puzovic and Hardy, 2007). The importance of developing a systematic approach to the study of drug incompatibility and stability in parenteral solutions is highlighted by the present study.

Establishment of an intravenous product's stability and compatibility with various intravenous solutions allows greater flexibility and convenience for administration. In general, antibiotics and PN admixtures should be administered through separate intravenous lines, however, in certain clinical situations it would be advantageous to mix the antibiotic in/with PN admixtures or to administer them in Y-site with PN admixtures (Zaccardelli *et al.,* 1990).

Previous studies addressing antibiotic compatibility with PN admixtures have used relatively dilute antibiotic solutions (i.e. ampicillin 1 mg/mL), or PN admixtures without electrolytes. Such data would only be valid for antibiotics administered in very low concentrations which is not useful especially when there is a need of high antibiotics doses (Mirtallo, 2004). This may be the reason for the different results of previous compatibility studies. Therefore, diluting each antibiotic dose in 50 to 100 mL of solution, as is often done in adult settings, may be acceptable. Unfortunately, we often do not afford the luxury of such fluid volumes in pediatric patients. The antibiotic infusion time and volume may also have an impact on the results (Niël-Weise *et al.,* 2008, Watson, 1985).

Parenteral Nutrition has become an accepted method for the administration of nutrients to patients. However, it is not without risks and complications (Dunham *et al.,* 1991). Patients