VALIDATION OF A DEVELOPED TOOL TO IDENTIFY COMPATIBILITY OF DRUG-DRUG AND DRUG-PARENTERAL NUTRITION IN NEONATES AND EVALUATION OF CLINICAL OUTCOME OF THE ADMINISTRATION OF THE IV DRUGS AND PARENTERAL NUTRITION

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by

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TABLE OF CONTENTS

Page

ACKNOWLEDGEMENT ii

TABLE OF CONTENTS iii

LIST OF FIGURES x

LIST OF TABLES xi

LIST OF APPENDICES xiv

LIST OF ABBREVIATIONS xv

ABSTRAK xvi

ABSTRACT xix

CHAPTER 1: INTRODUCTION 1

1.1 Background 1

1.2 Parenteral Nutrition in Malaysia 4

1.3 Problem Statement 5

1.4 Objectives of the Study 7

1.5 Hypothesis of the Study 8

1.6 Significance of the Study 9

CHAPTER 2: LITERATURE REVIEW 10

2.1 Nutritional Support 10

2.1.1 Oral Nutrition 10

2.1.2 Enteral Nutrition 10

2.1.3 Parenteral Nutrition 11

2.1.4 Parenteral Nutrition in Adult 12
2.1.5 Parenteral Nutrition in Pediatric 14
2.1.6 Parenteral Nutrition in Neonates 15
2.1.7 Component of Parenteral Nutrition 18
2.1.7 (a) Fluid 22
2.1.7 (b) Macronutrient 22
(i) Carbohydrate 23
(ii) Protein 25
(iii) Fat 28
2.1.7 (c) Micronutrient 30
(i) Electrolytes 30
(ii) Major Minerals 31
(iii) Trace Minerals 31
(iv) Vitamin 34
2.1.8 Complication Associated with Parenteral Nutrition 36
2.1.8 (a) Mechanical 36
2.1.8 (b) Metabolic 37
2.1.8 (c) Infections 40
2.1.9 Monitoring Parenteral Nutrition Efficacy 41
2.1.10 Administration of Drug with Parenteral Nutrition 43
2.1.11 Compatibility of Injectable Drug and Parenteral Nutrition 47
2.1.12 Incompatibilities and Interactions of Drug with Parenteral Nutrition 49
2.1.12 (a) Emulsion Changes 50
2.1.12 (b) Incompatibilities with the Bag Material 51
2.1.12 (c) Inactivation of Drugs or Parenteral Nutrition Components . 52

2.1.12 (d) Degradation Reactions Leading to Potential Activity 52
2.2 Drug Nutrient Interaction 53
2.3 Computer Application for Nutrient-Drug Interaction Management 57
2.3.1 Decision Support and Clinical Alert Systems in Drug Nutrient Interaction 58
2.3.2 Clinical Decision Support System for Neonatal Care 59
2.4 Development of Database My. Drug Compatibility Checker (My.DCC) 62
2.4.1 Introduction 62
2.4.2 Supporting Tools to Prevent Drugs Incompatibilities in Pediatric and NICU 63
2.4.3 Information Technology in Health the Malaysian Context 66

CHAPTER 3: METHODOLOGY 69
3.1 Introduction 69
3.2 Part I, Evaluation of Clinical Outcome of Parenteral Nutrition Practices 69
3.2.1 Study Design 69
3.2.2 Study Time and Location 69
3.2.3 Population and Sampling Procedure 70
3.2.4 Inclusion Criteria 70
3.2.5 Exclusion Criteria 70
3.2.6 Patient Data Collection Form 71
3.2.6 (a) Demographic Data and Birth History 71
3.2.6 (b) Disease and Treatment 71
3.2.6 (c) Intravenous Administration Data 71
3.2.6 (d) Laboratory Test 72

3.2.7 Ethical Clearance 72
3.2.8 Data Collection Procedure 72
3.2.9 Data Analysis 73
3.2.10 Study Flowchart 73
3.3 Part II, Development of My.DCC Database 75
3.3.1 Introduction 75
3.3.1 (a) Phase 1: Identify and Collecting the Compatibility Information of Drug –Drug and Drug - Parenteral Nutrition 75
3.3.1 (b) Phase 2: Develop Database 77
3.3.2 Tools Used in Development of My.DCC 78
3.3.3 Concept and Design 79
3.3.4 Design of Information Systems 79
3.3.4 (a) Conceptual Design 80
3.3.4 (b) Physical Design 80
3.3.5 System Design Tools 81
3.3.5 (a) Data Flow Diagrams (DFD) 81
3.3.5 (b) Entity Relationship Diagram (ERD) 81
(i) Entities 82
(ii) Attributes 82
(iii) Relation 82
3.3.5 (c) Hierarchy Process Input Output (HIPO) 83
3.3.6 Design of My.DCC 83
3.3.6 (a) General Design 83
3.3.6 (b) Data Flow Diagrams (DFD) 83

(i) Context Diagram……..83

(ii) Entity Relationship Diagram (ERD)……..84

(iii) Hierarchy Process Input Output (HIPO)……...87

3.3.7 Validation of My.DCC……87

3.3.7 (a) Validation of Content……...87

3.3.7 (b) Validation in Practice……88

CHAPTER 4: RESULT…….……..89

4.1 Introduction……..89

4.2 Evaluation…….....89

4.2.1 Demographic Data……...89

4.2.2 Birth Characteristic in Study Population…….91

4.2.3 Parenteral Nutrition Practices in NICU Patients…….97

4.2.4 Clinical Evaluation of NICU Patients……....103

4.3 Development and Validation of My. DCC……118

4.3.1 Identification of IV Drugs Commonly Prescribed in NICU……....118

4.3.2 Detailed Design of My. DCC Database……...120

4.3.2 (a) Output Design…….120

4.3.2 (b) Input Design……121

4.3.3 Validation of My. DCC Database……....123

4.3.3 (a) Time Validation to Retrieve the Data…….……123

4.3.3 (b) Validation of My. DCC Reporting System……125

4.4 Evaluation of Clinical Outcome in Patient with Incompatible Interaction……...130

4.4.1 Incompatibility of Drug – Drug and Drug - Parenteral Nutrition…….130

4.5 Comparison of Clinical Outcome in Patient with Incompatible and Compatible Interaction……...138

CHAPTER 5: DISCUSSION……..…144

5.1 Introduction…… ……144

5.2 Evaluation of Clinical Outcomes of Parenteral Nutrition in NICU Patients……144

5.3 Validation of a Developed Database My.Drug Compatibility Checker (My.DCC)…….151

5.4 Evaluation of Clinical Outcome of patients with Incompatible Interaction of Pediatric Injectable Drugs and Parenteral Nutrition…….154

CHAPTER 6: CONCLUSION, LIMITATION AND RECOMMENDATION…….157

6.1 Conclusion…….....157

6.2 Limitation of the Study……..158

6.3 Recommendations…….158

REFERENCES ……...159

APPENDIX A……..184

APPENDIX B……..185

APPENDIX C……..186

APPENDIX D……..187

APPENDIX E……..188

APPENDIX F…………………………………………………………………..189

APPENDIX G………………………………………………………………….190

LIST OF FIGURE

Page

Figure 2.1 Incompatibility reactions in Parenteral Nutrition……50

Figure 3.1 Study Flowchart. 74

Figure 3.2 Storyboard of Development Database. 77

Figure 3.3 Summary of Development of Database. 78

Figure 3.4 Diagrammatic Presentation of Tools and Requirement for Access. 78

Figure 3.5 Context Diagram of My.DCC..... 84

Figure 3.6 Entity Relationship Diagram (ERD) of My.DCC. 86

Figure 3.7 Hierarchy Input Process Output (HIPO) of My.DCC. 87

Figure 4.1 Drug Compatibility Result of My.DCC. 120

Figure 4.2 Drug Compatibility Result of Patient Treatment..... 121

Figure 4.3 Section to Update / Input of a New Drug Information 121

Figure 4.4 Section with Compatibility Information of Drugs in Syringe 122

Figure 4.5 Section with Compatibility Information of Drugs in Y-site Injection..... .122

Figure 4.6 Section to Update/Input of a New Patient 123

LIST OF TABLE

Page

Table 2.1 Indications for PN Support and Route of Administration for Neonates Who Require Intensive Care…….17

Table 2.2 Usual Daily Requirements of Nutrients in PN Solutions for Preterm and Term Neonates……18

Table 2.3 Amounts of Trace Minerals Recommended for Term and Preterm Infants in Total Parenteral Solutions (PN)……33

Table 2.4 Amounts of Vitamins Recommended for Term and Preterm Infants in PN Solutions Compared to PrescribedDosages of MVI-Pediatric.....35

Table 2.5 Nutritional Evaluation Parameters for Patients Receiving Parenteral Nutrition……42

Table 2.6 Metabolic Monitoring for Patients Receiving Parenteral Nutrition…..43

Table 2.7 Y-injection site Compatibility of Medications with Parenteral nutrition……...46

Table 2.8 Incompatibility Reactions…….49

Table 2.9 Summary of the Articles that Described Drug-Nutrient Interactions...55

Table 2.10 Summary of Different Supporting Tools to Identify The Compatibility of Pediatric Injectable Drugs…….65

Table 3.1 Self-developed Excel sheet of all the Pediatric Injectable Drugs and Compatibility Information……76

Table 3.2 Injectable Drug Used among NICU patients in Hospital Pulau Pinang……...76

Table 3.3 Symbols of DFD (Data Flows Diagram)……...……81

Table 4.1 Socio demographic Characteristic of the Study Population……...90

Table 4.2 Birth Characteristic of the patients…….91

Table 4.3 Comparison of Gender Differences among Various Variable of Birth History (n=234)……93

Table 4.4 Comparison of Race with Various Variable of Birth History (n=234)……95

Table 4.5 Comparison of Gestational Age and Various Variable of Birth History (n=234)……96

Table 4.6 Comparison of Birth Weight with Various Variable of Birth History (n=234)……97

Table 4.7 Descriptive of Parenteral Nutrition Practices among Study Population (n=234)…….98

Table 4.8 Comparison of Parenteral Nutrition Practices and Gestational Age (n=234)…….100

Table 4.9 Comparison of Parenteral Nutrition Practices and Birth Weight (n=234)……..102

Table 4.10 Concurrent Medical Problems among NICU Patients (n=234)….103

Table 4.11 Association between Gender and Concurrent Medical Problem among Patients (n=234)……..107

Table 4.12 Association between Race and Concurrent Medical Problem among Patients (n=234)……110

Table 4.13 Association between Gestational and Concurrent Medical Problem among Patients (n=234)……..113

Table 4.14 Association between Birth Weight and Concurrent Medical Problem among Patients (n=234)……116

Table 4.15 Descriptive Distribution of Intravenous Drugs Given during Parenteral Nutrition Administration. 119
Table 4.16 Comparison of the Time to Retrieve the Data. 124
Table 4.17 Compatibility Information of Injectable Drugs with Parenteral Nutrition Administration using My.DCC. 126
Table 4.18 Compatibility Information of Drug – Drug Interaction in Syringe and Y-site Administration using My.DCC. 127
Table 4.19 Compatibility Information of Injectable Drugs Combination in NICU. 130
Table 4.20 Evaluation of Incompatibility Drug - Parenteral Nutrition (2-in-1) in Y-site Administration 131
Table 4.21 Evaluation of Incompatibility Drug – Drug Combination in Y-site Administration……135
Table 4.22 Evaluation of Incompatibility of Drug-Drug Combination in Syringe…….. …….....137
Table 4.23 Demographic of Patients……139
Table 4.24 Comparison of Patient Clinical Diagnosis…….140
Table 4.25 Comparison of Parenteral Nutrition Practices……....141
Table 4.25 Comparison of Renal Function and Liver Function between Compatible and Incompatible Group……143

LIST OF APPENDICES

Page

Appendix A: Study Approval……...…..184

Appendix B: Patient Data Collection Form……..…...185

Appendix C: Letter of Agreement…….....186

Appendix D: Manual of My.DCC……...….187

Appendix E: My.DCC database……...188

Appendix F: Certificate of Proofreading..……..……..189

Appendix G: Publication List……...……190

LIST OF ABBREVIATION

CNS	Central Nervous System
CPAP	Continuous Positive Airway Pressure
DIVC	Disseminated Intra-Vascular Coagulation
ELBW	Extremely Low Birth Weight
G1P0	Gravida 1 Parity 0
G2P1	Gravida 2 Parity 1
G3P2	Gravida 3 Parity 2
HFOV	High Frequency Oscillatory Ventilation
HFPV	High Frequency Positive Ventilation
IMV	Intermittent Mandatory Ventilation
IVH	Intra Ventricular Haemorrhage
MVI	Multi Vitamin Injection
PDA	Patent Ductus Arterious
RDS	Respiratory Distress Syndrome
SGA	Small in Gestational Age

PENGESAHAN ALAT YANG DIBANGUNKAN UNTUK MENGENALPASTI KESERASIAN UBAT-UBAT DAN UBAT-NUTRISI PARENTERAL PADA NEONAT DAN PENILAIAN HASIL KLINIKAL PEMBERIAN UBAT IV DAN NUTRISI PARENTERAL

ABSTRAK

Pemberian ubat intravena di dalam Unit Rawatan Rapi Neonatal (NICU) adalah kritikal kerana kesulitan akses vena, polipengubatan, penghadan cecair dan kadar infusi yang rendah. Apabila Nutrisi Parenteral (PN) diinfusi secara intravena, ini telah dianggap sebagai pembawa kepada ubat. Ubat-ubatan boleh ditambah kepada formulasi PN dalam usaha untuk mengurangkan keperluan cecair, mengurangkan keperluan suntikan tapak-Y dan mengurangkan potensi kontaminasi salur akibat manipulasi serta mengurangkan masa yang diperlukan untuk menyuntik ubat. Walau bagaimanapun, risiko tetap tinggi akibat kekurangan maklumat tentang keserasian fizikokimia ubatan. Kajian ini bertujuan untuk menilai hasil klinikal pemberian drug IV dan PN di kalangan pesakit neonat yang menerima PN semasa dirawat di dalam hospital dan untuk membangunkan pangkalan data tentang keserasian drug-drug dan drug-larutan PN. Satu bentuk kajian Keratan Rentas Restrospektif telah digunapakai untuk menjalankan kajian ini. Subjek penyelidikan ini adalah pesakit neonat yang menerima PN di dalam Unit Rawatan Rapi Neonatal (NICU) Hospital Pulau Pinang, Malaysia. Subjek kajian merangkumi semua pesakit yang dimasukkan ke wad NICU daripada Januari 2008 hingga Disember 2009. Prosedur pensampelan adalah secara Pensampelan Umum dengan mengumpulkan semua rekod pesakit yang memenuhi kriteria kemasukan dan kriteria pengecualian yang ada. Sejumlah 234 bayi baru lahir yang telah memenuhi kriteria dimasukkan ke dalam kajian ini. Borang pengumpulan data dihasilkan penyelidik, telah digunapakai

dan hanya seorang pemungut data yang mengumpulkan data kajian. Kelulusan etika telah diperoleh dari institusi tempatan (Jawatankuasa Penyelidikan Klinikal, CRC) dan daripada Jawatankuasa Etika Penyelidikan Kementerian Kesihatan (MREC). Data dianalisa secara statisk menggunakan *Statistic Package for Social Science 15.0 (SPSS 15.0).* Kesemua 234 (100%) pesakit yang dimasukkan ke NICU Hospital Pulau Pinang dimasukkan ke dalam kajian ini. Daripada jumlah ini, majoriti 123 (52.6%) adalah perempuan dan selebihnya (47.4%) adalah lelaki. Taburan etnik menunjukkan Melayu mendominasi dengan 158 (67.5%) diikuti dengan Cina 41 (17.5%), India 23 (9.8%) dan lain-lain 12 (5.1%). Kebanyakan pesakit, 98 orang (41.8%) telah dilahirkan pada 28-31 minggu kandungan and 156 (66.67%) mempunyai berat badan di antara julat 1001-2000 gram. Ciri-ciri berkaitan pesakit (berat lahir, umur kandungan, mod kelahiran dan kaum-etnik) mempunyai perkaitan yang signifikan dengan amalan PN dan hasil klinikal. Satu pangkalan data dibangunkan iaitu "My. Drug Compatibility Checker (My.DCC)" yang memberikan maklumat keserasian berkaitan dengan interaksi drug-drug dan drug-PN bagi drug-drug IV yang sering dipreskrib untuk pesakit NICU. Pangkalan data My.DCC adalah alat yang sahih dan dipercayai untuk memberikan maklumat berkaitan keserasian dan interaksi drug-drug di dalam bahan tambahan larutan nutrisi parenteral. Konsep, rekabentuk dan isi kandungan yang diperlukan untuk prototaip ini telah dikaji, dikumpulkan dan disediakan oleh penyelidik. Seorang juru analisa sistem terlibat untuk membantu membangunkan peangaturcaraan sistem. Sebanyak 29 drug suntikan telah dianalisa menggunakan My.DCC. Pangkalan data ini telah digunakan untuk menyemak keserasian daripada kombinasi rawatan ubatan yang diterima oleh pesakit semasa di NICU Hospital Pulau Pinang. Penemuan My.DCC menunjukkan daripada 29 drug yang diberikan kepada pesakit; 4 kombinasi ubat adalah serasi di

dalam picagari, 2 kombinasi drug tidak serasi di dalam picagari, 25 kombinasi drug serasi dalam suntikan tapak-Y dan 8 drug tidak serasi dalam suntikan tapak-Y. Di kalangan pesakit, 19 neonat telah mengalami masalah keserasian interaksi drug-drug dan drug-nutrisi parenteral. Pengenalpastian interaksi drug-drug dan drug-nutrien dapat membantu ahli perubatan untuk mengelakkan komplikasi dan mencapai hasil yang disasarkan.

VALIDATION OF A DEVELOPED TOOL TO IDENTIFY COMPATIBILITY OF DRUG - DRUG AND DRUG - PARENTERAL NUTRITION IN NEONATES AND EVALUATION OF CLINICAL OUTCOME OF THE ADMINISTRATION OF THE IV DRUGS AND PARENTERAL NUTRITION

ABSTRACT

Intravenous drug administration in neonatal intensive care unit (NICU) is critical because of poor venous access, polymedication, fluid restriction and low infusion rate. Since parenteral nutrition (PN) is infused intravenously, it is often considered as a vehicle for medication administration. Medications may be added to PN formulations in an effort to decrease fluid requirements, reduce the need for Y-site injections, reduce the possibility of line contamination due to manipulation and decrease labor time required for drug administration. Risk is further increased by inadequate information on the physicochemical compatibility of drugs. This study aimed to evaluate clinical outcome of the administration of IV drugs and PN among neonates patients who had received PN during their hospitalization and to develop a data base on compatibility of drug-drug and drug-PN solution. A cross-sectional retrospective study design has been adopted to conduct this study. Subjects of this research were neonates' patients receiving PN in Neonatal Intensive Care Unit (NICU) Hospital Pulau Pinang, Malaysia. Study subjects were all patients admitted in NICU from January 2008 until December 2009. Sampling procedure was universal sampling by collecting all available patients' medical record that met our inclusion and exclusion criteria. A total of 234 newborn met the study criteria were included in this study. Self-developed data collection form was used with only single data collector for data collection. Approval for ethical clearance was obtained from

the local institutions (Clinical Research Committee, CRC) and from the Ministry of Health Research Ethics Committee (MREC). Data was statistically analyzed using Statistic Package for Social Science 15.0 (SPSS 15.0). All 234 (100%) patients admitted to NICU Hospital Pulau Pinang were included. Among them, majority 123 (52.6%) were females and the rest 111 (47.4) were males. Ethnic distribution showed predominance of Malay with 158 (67.5%) followed by Chinese 41 (17.5%), Indian 23 (9.8%) and 12 (5.1%) others. Most of the patients; 98 (41.8%) were born at 28-31 weeks of gestation and 156 (66.67%) were in the body weight range of 1001-2000 grams. Patient related characteristics (birth weight, gestation age, mode of delivery and ethnicity) have significant association with PN practices and clinical outcomes. A developed database "My. Drug Compatibility Checker (My.DCC)" will provide the compatibility information related to drug-drug and drug-PN interaction among IV drugs commonly prescribed in NICU patients. Database My.DCC consider as validate and reliable tool to provide information regarding compatibility and drug-drug interactions of admixture in parenteral nutrition solutions. The concept, design and contents required for this prototype were researched, collected and provided by researcher. One systems analyst was involved to carry out the programming of the system. The 29 injectable drugs had been analyzed with My.DCC. The database was used to check the possible compatibility of medication combination received during patient's treatment in NICU Hospital Pulau Pinang. The My.DCC finding showed that among 29 drugs that administered to the patients; 4 drugs combination were compatible in syringe, 2 drugs combination were incompatible in syringe, 25 drugs combination were compatible in Y-site injection and 8 drugs were incompatible in Y-site injection. Among them 19 neonates had incompatible interaction of drug-drug and drug-parenteral nutrition interaction. Recognition of these drug-drug and drug-

nutrient interactions may assist the clinician to prevent complications and to achieve desired therapeutics outcomes.

CHAPTER I

INTRODUCTION

1.1 Background

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, PN includes intravenous administration of amino acids, glucose, lipids, electrolytes, vitamins and trace elements (Dudrick, 2009, Waitzberg et al., 2006).

Patients who are receiving PN often need to receive parenteral medications as well. Questions about parenteral drug compatibility with PN have arisen with some frequency (Joy et al., 2010). Unfortunately, split administration is not always feasible. The line being used to administer PN constantly may be the only IV access accessible (Mirtallo, 2004). On the other hand, even if multiple lumen catheters are used, the numbers of parenteral doses required in high-intensity therapeutic situations, such as cancer treatment or intensive care may make simultaneous administration with a PN admixture (Hoang et.al 2008; Kearney et.al., 1998).

PN is a lifesaving medical intervention for many pediatric patients as PN 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).

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 glycaemia 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 and 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.at., 1995).

PN is one of the major advances in neonatal medicine, and it can be used successfully for prolonged periods in infants who cannot be fed enterally. Early use of PN can minimize the adverse impact of multiple metabolic complication in part because it provides multiple nutrients that may target a common metabolic function through different metabolic pathways. (NICE Guideline, 2006; Wilmore et.al, 1968). The early use of PN also helps to maintain an optimal nutritional states and allows the infant to better tolerate enteral feeding, which in turn is critical to the successful weaning of the

infant from PN. In contrast, inadequate nutritional support may contribute to a delay in growth over the short term (until hospital discharge) and over the long term by the persistence of growth delay into childhood, particularly in small preterm infants (ESPGHAN/ESPEN, 2005).

The addition of medications and other additives to PN 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). Above all, data about micronutrient stability after adding medication to pediatric PN 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 PN together with medications (Forbes, 2004).

The major obstacles encountered in delivering PN and medications in neonates are their limited intravenous access and fluid restriction. Fragile peripheral veins cannot withstand irritating chemicals in intravenous solutions and are often exhausted in a short period of time. The particular problem with drug therapy in infants is the consideration of fluid volume. Multiple drugs therapy for the acutely ill infant can account for a majority of the allowable fluid intake of the infant. When PN is used, the natural tendency is to use it as a drug delivery vehicle so as to remain within the fluid volume tolerance of the infant. Careful consideration must be given to the psychochemical properties of the drug and nutrient constituents to prevent incompatibilities and degradation or inactivation of certain nutrients in parenteral nutrition. (Niemiee et.al, 1984; Zenk et.al 1987).

1.2 Parenteral Nutrition in Malaysia

Prior to early eighties, parenteral nutrition in Malaysia was provided conventionally. Multiple nutritional solutions were hung over the patient's bed and administered by a multiple intravenous line. The indication for PN is mainly fluid therapy rather than as nutritional supplement (Bahari, 1994). Parenteral nutrition in Malaysia was first started at the Kuantan General Hospital in 1986, followed by the Penang Hospital, Kuala Lumpur Hospital and Universiti Sains Malaysia Hospital (Bahari, 1994; Shamsuddin et.al 1994; Bahari, 1998).

The role of pharmacists in the provision of PN services in Malaysian hospitals prior to 1986 had been very minimal. In fact, their main role was limited to the procurement and distribution of the nutritional solutions. PN services were started in Kuantan, Penang and Kuala Lumpur hospitals and followed by HUSM in 1987. HUSM provided the PN services initially to the pediatric wards and later expanded the services to include adult wards especially to surgical patients. In order to improve the role of pharmacists, HUSM started an Aseptic Dispensing Unit (ADU) within the Pharmacy Department in 1991 to provide a centralized PN service. The pharmacists from the ADU worked together with physicians, nurses and dietitians as a team known as TPN Team (Bahari, 1993).

1.3 Problem statement

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).

Intravenous drug administration in neonatal intensive care unit (NICU) and pediatric intensive care units (PICU) is critical because of poor venous access, polymedication, fluid restriction and low infusion rate. Risk is further increased by inadequate information on the physicochemical compatibility of drugs. Currently, no international guideline exists for the clinical management of drug incompatibilities. Different decision supporting tools such as handbooks, cross-tables and databases are available with essentially pertinent information about physical and chemical incompatibilities (De Giorgi et.al, 2010).

Since PN is infused intravenously, it is often considered as a vehicle for medication administration. Medication may be added to PN formulations in an effort to decrease fluid requirements, reduce the need for Y-site injections, reduce the possibility of line contamination due to manipulation and decrease labor time required for drug

administration. Although these reasons may seem compelling, the physicochemical complexity of PN formulations makes their interactions with parenteral medications a very challenging compatibility dilemma (Mirtallo et al., 2004).

Compatibility studies of medications with PN involve simulated 1:1 volume ratio dilutions of drug with PN admixtures, assuming the medication is administered via piggyback, intravenous push, or other intravenous method via the Y-site injection port (Driscoll, 2005). Actual concern is what happens in the tubing between the PN admixtures, Y-site, and venous catheter. A typical setback is an incompatibility that creates a precipitate or interrupts the fat emulsion stability resulting in an occluded catheter (Hoang et al., 2008; Kearney et.al 1998). Therefore, a drug that may appear to be compatible may have been altered considerably and lost most of its potency this way (Deshpande, 2003; Driscoll, 2003; Joy et al., 2010; Mirtallo, 2004).

A major disadvantage to the use of PN solutions as drug delivery vehicles is the lack of compatibility and drugs interaction data in the PN solutions that are used commonly in clinical practice. At present no study has been performed to develop tool or data base on drug-drug interactions and compatibility of PN solutions commonly used by hospital pharmacies in Malaysia.

The information necessary to address the above problem is still not available. Although the PN service has been introduced for more than 20 years in Malaysia, the data on the number of hospitals offering the service, the extend of pharmacists involvement, the availability of standard solution and other related information are

not available in a comprehensive manner (Bahari 1999; Shamsuddin et.al 1994; Bahari 1998; Bahari 1990; Harbans 1994; Ramanujam 1994). Drug nutrient interaction and physicochemical compatibility of cephalosporin with parenteral nutrition by using HPLC have been investigated (Shahid et.al 2013). Drug-nutrient interactions result in derangements of fluid and electrolyte homeostasis, changes in vitamin status, and disturbances of the acid-base balance. Recognition of compatibility and these drug-nutrient interactions may assist the clinician to prevent complications and to achieve desired therapeutics outcomes.

This study will develop and validate the database to provide compatibility information related to drug-drug and drug-PN interaction among IV drugs commonly prescribed in neonatal intensive care unit (NICU) patients in Malaysia setting. Development of this database is related to extend of PN practice in Malaysian Hospitals, the role of pharmacist and the scope of PN service. The study also will provide an evaluation of parenteral nutrition practice and clinical outcomes of critically ill neonates in neonatal intensive care unit Hospital Pulau Pinang.

1.4 Objectives of the Study

General objectives of the study were:

1. To develop a data base to identify the compatibility of drug-drug and drug-parenteral nutrition in NICU
2. To evaluate current parenteral nutrition practice in Neonates at Hospital Pulau Pinang

3. To validate the developed data base as a tool to check the compatibility of the drug-drug and drug-parenteral nutrition in NICU patients.

Specific objectives of the study were:

1. To evaluate socio demographic characteristic, clinical complication, parenteral nutrition practices and clinical outcome of the neonates receiving parenteral nutrition and injectable drugs
2. To identify IV drugs commonly prescribed during parenteral nutrition administration in neonate patients
3. To evaluate compatibility and clinical outcome of the neonates receiving parenteral nutrition and injectable drugs
4. To develop a database to identify the compatibility of drug-drug and drug-PN in NICU patients.

1.5 Hypothesis of the study

Hypothesis of the study was:

Ho: There is no association of clinical condition among neonates receiving parenteral nutrition and injectable drugs with the compatibility of drug-drug and drug-parenteral nutrition interaction.

1.6 Significance of the study

1. The study will contribute in the improvement of quality of nutritional care of neonatal intensive care patients by reducing the risks of drug-drug and drug-nutrient interactions of PN formulation.

2. The databases can be used to develop guideline in prevention of drug-drug or drug-parenteral nutrition interactions.

CHAPTER II

LITERATURE REVIEW

2.1 Nutritional support

2.1.1 Oral nutrition

Oral supplements should be prescribed for those unable to meet their nutritional requirements from the hospital menu. These supplements are available in a variety of flavours such as in semi-solid or powder form, as well as cartons of liquid. Verbal encouragement, offering a mix of flavours and giving them chilled or as a milkshake aids compliance (ASPEN 2002).

2.1.2 Enteral Nutrition

All people need food to live, however sometimes a person cannot eat any or enough food because of an illness while others may have a decreased appetite, difficulties in swallowing, or some types of surgery that interferes with eating. When this occurs, and one is unable to eat, nutrition must be supplied in a different way. One method is "enteral nutrition" often called "tube feeding". Tube feeding is a method in which a special liquid food formula containing protein, carbohydrates (sugar), fats, vitamins and minerals, is given through a tube into the stomach or small bowel. People of all ages have received tube feeding. It may be given to infants and children, as well as to adults. Tube feeding can be used for a short time, and then the tube is removed when the person can begin to eat normally again. Tube feeding can be given through different types of tubes. One type of tube can be placed through the nose into the

stomach or small bowel. This tube is called a nasogastric or nasoenteral feeding tube. Sometimes the tube is placed directly through the skin into the stomach or small bowel. This method is called a gastrostomy or jejunostomy (ASPEN 2002; ASPEN 2009).

If the patient is unable (e.g. nausea, frailty) to drink nutritional sip feeds, enteral tube feeding should be considered. The benefits of enteral tube feeding include: nutrients are effectively mobilized and utilized as compared to parenteral feeding, function of the gut barrier is preserved, preventing 'bacterial translocation' can be prevented, hence reducing the chance of sepsis, complications are generally less serious than those of parenteral nutrition, and it is also cheaper and easier to manage than parenteral nutrition. Choice of enteral tube feeds depends on: the route of nutritional support, nutritional requirements, impairment of the gastrointestinal tract and associated clinical conditions (e.g. renal or liver failure) (Merce et.al, 2002).

2.1.3 Parenteral Nutrition

Parenteral nutrition (PN) is intravenous administration of nutrition, which may include protein, carbohydrate, fat, minerals and electrolytes, vitamins and other trace elements for patients who cannot eat or absorb enough food through tube feeding formula to maintain good nutrition status. Achieving the right nutritional intake in a timely manner can help combat complications and be an important part of a patient's recovery (ASPEN 2009).

Parenteral nutrition is sometimes called Total Parenteral Nutrition (PN). People of all ages also receive parenteral nutrition. Like tube feeding, it may be given to infants and

children, as well as to adults. People can live well on parenteral nutrition for as long as it is needed. Many times, parenteral nutrition is used for a short time; then it is lessened or discontinued when the person begins to eat normally again. Parenteral nutrition bypasses the normal digestion in the gastrointestinal (GI) tract. It is a sterile liquid chemical formula given directly into the bloodstream through an intravenous (IV) catheter (needle in the vein). Patients may need PN for any variety of diseases or conditions that impair food intake, nutrient digestion or absorption. Some diseases and conditions where PN is indicated include but are not limited to short bowel syndrome, GI fistulas, bowel obstruction, critically ill patients, and severe acute pancreatitis. Some patients may require this therapy for a short time and there are other patients who have received TPN at home for a lifetime. PN is a life-saving yet complex therapy, which is not without risk of complications. Some of these complications include infection, metabolic, and fluid issues. Management by an interdisciplinary Nutrition Support Team can optimize patient outcomes associated with this therapy (ASPEN 2009; JPEN 2004).

Failure of enteral feeding is the main indication for parenteral nutrition. Enteral tube feeding is inappropriate in proximal intestinal fistulas, intestinal obstruction or post-chemotherapy mucositis. Total intravenous feeding is commonly used. Long-term parenteral nutrition is well established and can be delivered at home safely and with an excellent quality of life (JPEN, 2004)

2.1.4 Parenteral Nutrition in Adult

Parenteral nutrition refers to TPN formulations; total nutrient admixtures (TNA) are TPN formulations that include intravenous fat emulsion (IVFE); and 2 in 1

formulations are TPN formulations that do not include IVFE. PN formulations are extremely complex admixtures containing 40 or more components including both macronutrients (carbohydrates, lipids, amino acids) and micronutrients (electrolytes, trace minerals and vitamins). These nutrients are mixed into a bag and infused simultaneously into the blood circulation through the peripheral or central vein. (Maisonneuve et.al, 2004; Mirtallo et.al 2004).

PN is indicated in patients with a non-functioning digestive tract to correct or maintain their nutritional status. They can be administered in any of the following ways: firstly, the classic separate bottles (SB) system in which nutrients are stored in separate bottles or bags and infused through separate intravenous (IV) lines. This system requires numerous IV line manipulations and is associated with increased risk of administration errors, as well as septic and metabolic complications. Secondly, the 'all-in-one' system in which all nutrients are mixed in one bag and infused simultaneously. This system requires only one IV line, thus decreasing manipulation-related and metabolic risks. Thirdly, three-compartment bags containing macronutrients and electrolytes in three separate compartments. Nutrients are mixed just prior to infusion, by breaking the plastic connectors between the compartments, and then vitamins and trace elements are added extemporaneously to the bag. The shelf-life of these bags is at least 12 months, but it is only useful for standardized formulas. PN provides life-sustaining therapy for patients who are unable to consume conventional dietary therapy either orally or enterally (Maisonneuve et.al 2004; Riyadh et.al, 2007).

Nowadays, the term PN is widely used in the literature to denote the administration of nutrients intravenously. Basically, PN is only indicated when the oral, or enteral, route of nutrition cannot be established (i.e. the use of the gastrointestinal system), or is insufficient for the maintenance of the patient's nutritional requirements in relation to his/her clinical status. Partial parenteral nutrition is the concurrent IV administration of nutrients together with oral or enteral nutrition for the same therapeutic objective. The dietary components of a standard PN regimen are the macronutrients (protein or amino acids, carbohydrates and fats), the electrolytes, the micronutrients (trace elements and vitamins) and water. Carbohydrates, in the form of glucose or dextrose, and lipids are the major sources of energy (Shamsuddin et.al, 2003).

2.1.5 Parenteral Nutrition in Pediatric

PN is used to treat children that cannot be fully fed by oral or enteral route, for example due to severe intestinal failure (Wilmore et.al, 1968). Intestinal failure occurs when the gastrointestinal tract is unable to ingest, digest and absorbs sufficient macronutrients and/or water and electrolytes to maintain health and growth. Children differ from adults in that their food intake must provide sufficient nutrients not only for the maintenance of body tissues but also for growth. This is particularly true in infancy and during adolescence when children grow extremely rapidly. At these times children are particularly sensitive to energy restriction because of high basal and anabolic requirements (Heird et.al 1972; Koletzko et.al, 2005).

The ability to provide sufficient nutrients parenterally to sustain growth in infants and children suffering from intestinal failure or severe functional intestinal immaturity represents one of the most important therapeutic advances in pediatrics over the last three decades. Improvements in techniques for artificial nutritional support now ensure that children in whom digestion and absorption are inadequate or who are unable to eat normally no longer need to suffer from the serious consequences of malnutrition including death. (Tsang et.al 2005; Royal College of Pediatrics and Child Health, 1997).

2.1.6 Parenteral Nutrition in Neonates

Total parenteral nutrition (PN) is the intravenous infusion of all nutrients necessary for metabolic requirements and growth. PN refers to the supplemental intravenous infusion of nutrients by peripheral or central vein. Enteral nutrition (EN) is provided by oral or gavage feedings. PN is commonly indicated in neonates experiencing congenital malformation of the gastrointestinal tract, gastroschisis, meconium and paralytic ileus, short bowel syndrome, necrotizing enterocolitis (NEC), respiratory distress syndrome, extreme prematurity, sepsis, and malabsorption. The ability to provide PN over the past four decades has significantly improved the overall survival of newborns when other options of adequate nutritional support were not possible (Brine et.al, 2004).

The goal of PN is to initially provide sufficient nutrients to prevent negative energy and nitrogen balance and essential fatty acid deficiency and support normal rates of intrauterine growth of appropriate composition without increased significant

morbidity. Fear of toxicity and metabolic imbalance has alerted clinicians to use PN with caution, especially in the sickest and most premature infants. An increasing number of practitioners appreciate that this cautionary management has resulted in suboptimal nutrition intake of these infants. Practitioners have speculated that this cautionary practice contributed in part to national growth failure outcome statistics published of infants extremely low in birth weight (ELBW; less than 1,000 grams) and appropriate for gestational age (AGA; weight $\geq 10^{th}$ percentile norm) born from 1995 to 1996. When assessed at discharge (≈ 36 weeks' corrected age) 99% of these infants had significant growth failure with weights less than the 10th percentile compared with intrauterine growth standards.(Brine et.al 2004; Lemons et.al 2001) Longer-term statistics indicate that a significant percentage of infants born very low in birth weight (VLBW; less than 1,500 grams) may suffer substantial neurodevelopmental deficits in part attributable to inadequate nutritional support in the neonatal period.(Hack et.al, 1999) In more recent years, the earlier introduction and more aggressive advancement of TPN was shown to be safe and effective, even in the smallest and most immature infants (Thureen et.al 1999; Thureen et.al, 2000; Thureen et.al 2003, Heird et.al 1999, Poindexter et.al 2003).

Timely intervention with PN begins with the provision of glucose as soon as possible after birth with amino acids within the first 12 hours, intravenous fat within the first 24 to 48 hours, and trophic feeding within the first 24 hours. (Wilson et.al 1997). Optimal use of routine PN for nutritional support of ELBW and VLBW infants may influence short-term outcomes such as lower propensity to infection and shortened hospital stay, as well as longer-term outcomes such as decreased growth deficits improved neurodevelopment, and overall morbidity (Hay et.al 1999; Dusick et.al,

1998; Vohr et .al, 2000). Indications that are generally recognized as those that necessitate PN for newborns are listed in Table 2.1.

Table 2.1 Indications for PN Support and Route of Administration for Neonates Who Require Intensive Care (adapted from Brine E and Ernst J (2004), *Newborn and Infant Nursing Reviews,* 4, 133-155.)

Route of PN Administration	Indication for PN
Peripheral	Temporary supply of nutrients <2 weeks: - Less Enteral intake - Functional gut immaturity - Temporary feeding intolerance - Medical instability
Central	Prolonged nonuse of the gastrointestinal (GI) tract >2 weeks: - Short bowel syndrome - Surgical GI disorders - Necrotizing enterocolitis - Intractable diarrhea - Meconium ileus - Line access in infants extremely low in birth weight <1,000 grams

2.1.7 Components of PN Solutions

PN provides some or all nutrients of basal metabolism and growth for fluid, energy, macronutrients(protein, carbohydrate, and fat) and micronutrients (electrolytes, major minerals, trace minerals, and vitamins) (Price et.al 2000; Anderson et.al 2000; Ziegler et.al 1976; Peter 1997; Yardley 1992; Vileisis 1987; Schanler 2003; Krug 2000). Recommended intakes for premature and term neonates are summarized in Table 2.2:

Table 2.2 Usual Daily Requirements of Nutrients in PN Solutions for Preterm and Term Neonates (adapted from Brine E and Ernst J (2004), *Newborn and Infant Nursing Reviews,* 4, 133-155.)

Nutrient Additive	Usual Daily requirements in PN
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) 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
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 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
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	400µg/kg/d: Preterm infants and all infants with gastrointestinal losses 250µg/kg/d: Term infants 0-3 months 100µg/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 0.05µg/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: 1.0µg/kg/d
Molybdenum (Mb)	Withhold for the first 3 months of TPN Decrease amount or withhold with complication of renal dysfunction Premature/term: 0.25µg/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: 1.0-2.0µg/kg/d
Fluoride (Fl)	Withhold for the first 3 months of TPN then provide premature with 500µg/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 2.2.

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 PN 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)

2.1.7 (a). Fluid

On day one of life, maintenance of fluids are met with arrangement between 80 and 140 mL/kg/d if the environment of the baby increases insensible water losses and 60 to 100mL/kg/d in environments with increased humidity. Thereafter, fluid volume is advanced as tolerated to 120 to180 mL/kg/d. Maximal fluid volume varies with individual management (Anderson 2000).

2.1.7 (b). Macronutrients

Carbohydrate (dextrose) and fat (lipid emulsions) provide the energy needed to meet the demands of the circulatory, respiratory, neurological, and muscular systems and,

when provided in adequate amounts, spare protein(amino acids) to support cell maturation, remodeling, growth, activity of enzymes, and transport proteins for all body organs. Energy needs may be increased with infection, chronic lung disease, healing, growth, and in neonates who have experienced intrauterine growth restriction (IUGR). Energy needs may be decreased with sedation, mechanical ventilation, and after tracheotomy placement.

The use of PN is suggested to support all ill and premature neonates less than 1,500 grams that cannot sustain at least ~60 kcal/kg/d enterally and initiation isrecommended during the first 24 hours of life to avoidexcessive protein losses. The premature infant who is not growing, not septic, and not unduly stressed requires an energy intake of about 50 kcal/kg/d for resting energy expenditure, activity, and occasional cold stress, (Denne et.al 2002; Leitch et.al 2000; Zlotkin et.al 1981; Bell 1996) with as little as ~1 to 1.5 g protein/kg/d to preserve endogenousprotein stores (Thureen et.al 2003; Ziegler 1994; Thureen et.al 1998). At least 60 kcal/kg/d is thought to meet energy requirements during acute sepsis (Premer et.al 1999).

(i). Carbohydrate

Carbohydrate is delivered in 2.5 to 70% dextrose solutions that provide 3.4 kcal/g. Glucose is the energy source for all cells and is essential for the central nervous system (CNS), erythrocytes, and other tissues. To ensure a stressed premature infant receives an adequate but not excessive amount of glucose, the amount of carbohydrate delivered in the form of dextrose is commonly initiated at the endogenous hepatic glucose production and utilization rate of 4 to 6 mg/kg/min (Denne et.al 1986) 8 to 10

mg/kg/min in ELBW infants provides 40 to 50kcal/kg/d and preserves carbohydrate stores (Hertz et.al 1993).

Frequently smaller, more unstable premature infants develop hyperglycemia due to decreased insulin production and insulin resistance. Glucose infusion rates (GIR) for these neonates may need to be limited to 4 mg/kg/min or less, while larger preterm infants or term infants can often tolerate up to 8 mg/kg/min initially (Denne et.al 2002; Lifshitz 1988). Once the GIR supports acceptable serum glucose values, it is advanced in a gradual, stepwise fashion (0.5 to 1 mg/kg/min) to a suggested maximum glucose oxidative rate for neonates of 12 to 13 mg/kg/min to support growth and maintained there unless serum glucose values change significantly (Reiter et.al 2001; Baker et.al 1997).

In most situations, a glucose concentration above12.5% is not necessary (Denne et.al 2002). However a higher glucose concentration may be needed when fluid intake is severely restricted or when the amounts of protein and/or fat are limited (Denne et.al 2002). Excessive carbohydrate delivery above the amount that can be oxidized for energy and glycogen storage will lead to an increase in basal metabolic rate (Kanarek et.al 1991) fat deposition, cholestasis (Henry, 2003), hepatic steatosis (Shulman 2000) or over feeding as described by the provision of energy in excess of needs for normal growth (Shulman 2000). GIR greater than 26 mg glucose/kg/min may contribute to infiltrates of fat in the liver (Pediatric Nutrition Handbook 2004).