CHAPTER II

LITERATURE REVIEW

Malnutrition is common in hospital patients, but sometimes clinicians fail to recognise it. Consequently, many patients do not receive appropriate treatment. This is one reason why nutrition status declines in the majority of patients who are admitted to hospital, with detrimental effect on clinical outcome. Feeding patients with adequate nutrition is an important component of medical care.

Since the late 1960's, when Dudrick first demonstrated the efficacy of long-term parenteral nutrition (PN) for patients in whom gut feeding is not feasible, the indications for this therapy have expanded as our knowledge has increased. New skills are needed to properly feed the right patient at the right time and in the right route. This requires cross training among physicians, nurses, dietitians, pharmacists, and other workers, to consider for providing parenteral nutrition support for the patients (Driscoll, 2003).

2.1 Parenteral Nutrition

PN is a life-saving art. Pre- and post-surgical management of the emaciated or difficult-to-nourish patient has been greatly facilitated by the ability to feed this patient completely while bypassing the gastrointestinal (GI) tract. PN ideally includes the intravenous (IV) administration of nutrients in amounts sufficient to achieve tissue synthesis and an anabolic state in the severely ill when oral ingestion is not possible or not adequate alone. PN therapy is physiological effective, sustaining and even improving normal nutritional status during short-term needs or over long periods of time while underlying disease is being treated, and in medical emergencies. It is of

value in maintenance of noningesting patients preparatory to surgery and others with debility or dysfunction of the GI tract (Rombeau and Caldwell, 1986).

2.2 Indications of Parenteral Nutrition

PN should be used when the GI tract is not functional or cannot be accessed and in patients who cannot be adequately nourished by enteral nutrition. Table 1 shows the general considerations for the use of PN. In pediatrics, long-term PN can support normal growth and development. Table 2 list some conditions in which PN is necessary to fully support the infant or child. To be a guideline for use of PN in hospitalized patients, American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) stated the PN indication for specific disease. It is concluded that PN is used in patients whose GI tract cannot be used for prolong period, who cannot be fed enterally, who has hypermetabolism, and who has eating disorder (A.S.P.E.N., 2002).

Table 1 General Consideration for the Use of PN (Shikora and Blackburn, 1997)

1. Interruption of oral alimentation for greater than 7 – 10 days (less than 7 days for patients with compromised nutritional stores and / or severe catabolic illness.)
2. The inability to utilize the gastrointestinal tract to provide nutritional support.
3. The ability to establish stable intravenous access.
4. The ability to formulate an appropriate TPN solution.

Table 2 Nutritional Risk Factors as an Indication for Immediate Nutrition Support (Baker, et al., 1997)

Low birth weight infant who immature gastrointestinal function
Prematurely born infant
Weight loss more than 10 % of usual body weight
Decrease in tow growth channels within 1 – 4 weeks
No weight gain for 3 months or more
Serum albumin less than 2.8 g / dL
Partially Functional
Cannot meet nutrient requirements after maximize enteral support
Burns
Multiorgan failure
Short small bowel, intractable diarrhea, villous atrophy, dysmotility syndromes
Risk of aspiration when small bowel feedings are not possible
Malnutrition with hypoproteinemia
Nonfunctional
Paralytic ileus
Chronic intractable vomiting when small bowel feedings are not possible
Small bowel ischemia
Necrotizing enterocolitis
Severe acute pancreatitis
Gastrointestinal surgery
Gastroschisis, omphalocele, multiple intestinal atresias, etc., until the enteral route is accessible
Severe inflammatory bowel disease with possible impending surgery

2.3 Route of Parenteral Nutrition Administration

There are two routes of PN administration including peripheral and central routes.

2.3.1 Peripheral Route (Shikora and Blackburn, 1997)

Peripheral PN (PPN) solution is infused through a peripheral vein usually the largest available forearm vein. PPN is used to partially or totally meet nutrient needs in patients unable to do so by the oral or enteral route, or when central access is not feasible. PPN is usually reserved for patients requiring short-term PN who are not markedly hypermetabolic or fluid restricted and have adequate peripheral venous access. Candidates for PPN may include patients with gastrointestinal disorders or

who has limited nutrient intake on a short-term basis generally less than 10-14 days until oral feeding can be resumed or central PN is needed; who has a high risk of catheter sepsis or who has previously on central access and had removed secondary to sepsis or complications; who has mild metabolic stress or mild pre-existing malnutrition; who has good peripheral venous access.

Osmolarity and compatibility are factors that need to be considered in PPN solutions. Infusion of hypertonic solutions through a peripheral vein may result in phlebitis. The amount of dextrose and amino acids in the solution is generally limited due to the contribution they make to its osmolarity. Although fluid volume of the solution can be increased to reduce osmolarity, this may not be practical or safe in many patients. PPN usually does not provide adequate calories and protein for hyper metabolic, fluid–restricted patients but can be helpful for several days until GI function returns or central access is obtained. Peripheral IV access can only be used when infusing solutions less than 900 mOsm/L. There are several advantages associated with the use of PPN such as easily access of peripheral line unless by non surgical personnel; minimize serious complications when avoiding TPN uses; does not require tapering when discontinuing; provide less expensive and less complex than TPN; can provide preoperative nutrition support; provide more efficient protein sparing than the more traditional administration of 5% dextrose in water.

2.3.2 Central Route

In order to administer hypertonic solutions safely and prevent such damage to veins, a central venous catheter must be used. The two great veins most often used for central venous access are the subclavian and internal jugular veins. However, the insertion of a catheter into the central venous system is associated with the risk of a number of serious complications including air embolism, hemothorax and infection (Brogden, 2004). In conclusion, Central PN is usually indicated in patients who

require long-term parenteral nutrition; who have specific nutrition requirement or fluid restriction; who already have central venous access established; who have failed with PPN or peripheral access (Payne-James, Grimble and Silk, 2001).

When considering a suitable venous access device, the benefits and risks to the patients must be assessed. Choosing an appropriate device will enable safe administration of therapeutic agents such as PN. It may also improve the patient's quality of life and hospital stay.

2.4 Parenteral Nutrition Monitoring (Reily, 1998; Brogden, 2004)

2.4.1 Clinical Monitoring

Initially the patient should be carefully observed for signs of pneumothorax and other mechanical complications that can occur as a complication of line insertion. The correct position of the line must be confirmed on X-ray. Thereafter, the line should be checked daily for sign of damage or displacement. Line infection or sepsis must be closely monitored, by checking the white cell count regularly. Blood pressure, pulse, respiration rate, and temperature should be checked 6-hourly. The line assessed with cultures if line infection is suspected. Weight should be measured daily as a guide to fluid changes, and detailed, accurate fluid balance charts should be kept. Blood glucose monitoring should be carried out 6-hourly, increasing to 1 – 2 hourly if glucose level is unstable or insulin is required.

2.4.2 Biochemical Monitoring

Initially, urea and electrolytes should be checked daily. Serum lipid levels, acid – base balance, electrolyte levels and liver function tests should be carried out on initiation of PN and be checked daily until the patient's condition is stable. Assessment of trace element status is also recommended in nutritionally depleted patients and in long-term PN.

2.4.3 Nutritional Monitoring

Comparison of weekly weights will give a guide to the patient's nutritional status, but fluid balance must also be taken into account and can make results difficult to interpret. Mid-upper arm anthropometry can be used to assess long-term changes in lean body mass and fat reserves. Table 3 shows suggested monitoring parameters and schedule during pediatrics and adults.

2.4.4 The Role of Nutrition Support Teams

(Grant, 1992; Payne-James, et al., 2001)

The presence of a nutrition support team improves clinical outcomes among patients on IV feeding such as, reduces incidence of complications; ensures more regular and appropriate biochemical and nutritional monitoring; achieves nutritional goal; improves quality of care; reduce cost of hospital stay. Most successful PN teams include clinicians, dietitians, nurses, and pharmacists. Chemical pathologists, and microbiologists are also important and can be include if available.

2.4.4.1 The nurses

The nurses have a key role in nutrition support team. They have the great advantage of being able to go on to most wards and encourage participants in the nursing process and ward routines to detect, monitor and treat malnourished patients. The nurses have an essential role in educating ward nurses on the importance of a nutritional history and taking measurements such as height and weight during the admission procedure. The nurses may change IV feeding bag and care for the intravenous line according to standard protocols.

2.4.4.2 The dietitians

The dietitians who are interested in active patient care and are knowledgeable in special dietary formulas are essential for the nutrition support team.

Table 3 Suggested Monitoring Parameters and Schedule During Parenteral Nutrition (Baker, et al., 1997)

Parameter	Suggested Frequency	
	Initial / Hospitalized	**Follow – up / Home**
Growth		
Weight	Daily	Daily to monthly
Height / length	Weekly	Weekly to monthly
Head circumference	Weekly	Weekly to monthly
Body composition	Monthly	Monthly to annually
Metabolic (serum) [a]		
Electrolytes	Daily to weekly	Weekly to monthly
Bun / Creatinine	Weekly	Monthly
Ca, PO_4, Mg	Twice weekly	Weekly to monthly
Acid – Base status	Until stable	Weekly to monthly
Albumin / prealbumin	Weekly	Weekly to monthly
Glucose	Daily to weekly	Weekly to monthly
Triglycerides	Daily while increasing lipid	Weekly to monthly
Liver function tests	Weekly	Weekly to monthly
Complete blood count / differential	Weekly	Weekly to monthly
Platelets, PT / PTT	Weekly	As indicated
Iron Indices	As indicated	Biannually to annually
Trace elements	Monthly	Biannually to annually
Fat soluble vitamins	As indicated	Biannually to annually
Carnitine	As indicated	As indicated
Folate / vitamin B_{12}	As indicated	As indicated
Ammonia	As indicated	As indicated
Cultures	As indicated	As indicated
Metabolic (urine)		
Glucose	2 to 6 times / day	Daily to weekly
Ketones	2 to 6 times / day	Daily to weekly
Specific gravity	As indicated	As indicated
Urea nitrogen	As indicated	As indicated
Clinical Observation (activity, vital signs [b]**)**	Daily	Daily
Developmental milestones	As indicated	Annually
Intake and output	Daily	Daily to as indicated
Administration system	6 to 12 times / day	2 to 6 times / day
Catheter site / dressing	6 to 12 times / day	2 to 6 times / day

Note: Frequency depends on clinical conditions.

[a] For metabolically unstable patients may need to check more frequently.

[b] Vital signs include respiratory rate, heart rate, temperature, and blood pressure.

They have a key role in collaboration with the nurse in assessing and monitoring nutrition intake. The dietitian can then advise on how best to remedy deficiencies in diet. The dietitians can firstly evaluate patient's nutritional status, determination of the degree of stress, and estimation of nutritional needs. The dietitians are responsible for continued monitoring of each patient's nutritional status to ensure that changing metabolic needs are recognized and met. At the conclusion of therapy, they evaluate the adequacy of the course of nutrition support, making a determination as to whether that course was successful in meeting the patient's needs, thereby, maintaining or improving the patient's nutritional status.

2.4.4.3 The physicians

The physicians involved in the team can also take responsibility for insertion of IV feeding lines. They can also ensure that an IV feeding regimen is prescribed which meets the needs of the patient and fits in with the other care being provided by the team that is ultimately responsible for the patient. They make rounds daily on all patients and are available 24 hours a day for evaluation and management of any complications.

2.4.4.4 The pharmacists

The involvement of a pharmacist is extremely valuable in a number of ways. First of all, the pharmacist can gently direct inexpert physicians, who feel that they should provide IV feeding for a patient, to the nutrition support team for advice. This may result in safer and cheaper enteral nutrition being used rather than IV nutrition. When IV nutrition is required, the pharmacist can formulate and prepare the feed. It is essential that the mixture is stable until infusion has been completed and that is prepared in a strictly aseptic manner. Both of these require pharmaceutical manufacturing skills and facilities. They are available 24 hours a day for solution related problems and drug-nutrient interaction identifications.

2.5 Complications of Parenteral Nutrition

Despite careful planning, advancement and monitoring, PN has a number of potential complications. Complication can be classified into 4 categories: infectious, mechanical, metabolic / nutritional, and psychosocial complications (Baker, et. al., 1997).

2.5.1 Infectious Complications

Infections are the most common complications that are generally catheter – related. Definition of catheter-related infections are the presence of bacteremia most commonly associated with catheter infection either at the skin insertion site or the catheter tip, or contamination of parenteral nutrition itself. In this latter situation, the organisms isolated are usually quite unusual bacteria found only rarely as a common isolate in surgical site infections. Infection of the catheter insertion site is defined by the presence of pus, a semi-quantitative culture of ≥ 15 colonies from an inoculation from fluid obtained from around the insertion site, or a semi-quantitative culture of the subcutaneous portion and/or tip of the TPN catheter with $\geq 10^3$ colonies per agar plate. Catheter-related bacteremia is presented when cultures from both peripheral blood and the catheter are positive for the same microorganism without any obvious site of infection. The main causal infective agents involving primarily gram-positive bacteria, gram–negative bacteria, fungi and even mycobacteria are shown in Table 4.

Several factors predispose to catheter infections. The number of lumens available for use within the catheter is one of the risk factor for infection, using a single lumen catheter whenever possible is recommended. Site of catheter insertion and type of placement procedure used are the higher risk of infection. The least risk of infection occurs when the catheter is placed in the upper extremity, followed by the subclavian, cervical, the femoral region; similarly, the least risk of infection occurs with a percutaneous insertion technique as opposed to operative 'cut down'. Improper

aseptic technique can lead to infectious complication. Educated and trained staff can reduce this complication cause. Septic complications associated with PN can be prevented by the use of 0.22 μm filters for filtering particulates and should be done in the pharmacy during compounding under LAFH by aseptic techniques. Currently, the accepted initial treatment for catheter–related infections involves the aggressive administration of broad–spectrum antibiotics; use of antibiotics administered only once or twice daily may be best to minimize catheter manipulation; administering a highly concentrated antibiotic solution in an amount sufficient to fill the internal lumen of the catheter twice daily. This approach was successful in > 90 % of patients with catheter– related infection (Montalvo-Jave, Zarraga, and Sarr, 2007)

Table 4 Most common organisms causing catheter-related PN infections (Montalvo-Jave, et. al., 2007)

Bacteria gram (-)	Bacteria gram (+)	Fungi	Mycobacteria
Escherichia coli	*Staphylococcus aureus*	*Candida albicans*	*Mycobacterium avium*
Pseudomonas aeruginosa	*Enterococcus durans*	*Candida glabrata*	*Mycobacterium chelonae*
Klebsiella pneumoniae	*Streptococcus viridans*	*Candida guilliemondii*	*Mycobacterium fortiutum*
Enterobacter cloacae	*Peptostreptococcus*	*Candida parapsilopsis*	*Mycobacterium xenopi*
Acinetobacter diversus	*Propionibacterium*	*Candida tropicalis*	
Citrobacter freundii	*Streptococcus faecalis*	*Mallessezia furfur*	
Citrobacter diversus	*Enterococcus faecalis*		
Acinetobacter antitritus	*Corynebacterium* spp.		
Lactobacillus spp.	*Staphylococcus hominis*		

Sign of sepsis include lethargy, hyperbilirubinemia (in the neonate), temperature instability, and intolerance to parenteral substrates that were previously tolerated. When the patient develops sign of sepsis, the catheter should be replaced initially by a new catheter and with culture of the distal and proximal ends of the suspect catheter and PN for detecting source of infection, and type of the main causal bacteria, then proper antibiotics are given (Baker, et al., 1997; Montalvo-Jave, et al., 2007).

2.5.2 Mechanical Complications

Mechanical complication can be divided into 2 parts: the catheter–related and the vascular complications. The most common causes of this complication type are the wrong catheter insertion technique, or inadequate understanding or poor supervision of the technician that can result in devastating complications. Mechanical complications include pneumothorax, subclavian artery injury, catheter malposition, air embolism, thrombosis of central vein, catheter occlusion, perforation and infusion leak, in fusion system obstruction, and phlebitis (Baker, et al, 1997, Montalvo-Jave, et al., 2007).

2.5.3 Metabolic Complications

Metabolic complications are caused by a patient's intolerance of one or more constituents in the PN solution. Metabolic complications include refeeding syndrome, hepatic steatosis, cholelithiasis, osmotic diuresis, hyperammonemia, azotemia, hyperglycemia, metabolic alkalosis, fluid overload, respiratory acidosis, cholestasis, electrolyte imbalances, essential fatty acid deficiency, rash, hypertriglyceridemia, trace element deficiency, vitamin disorders, and manganese toxicity. In long-term PN, gut immune function decreased and bone disease could occur (Btaiche and Khalidi, 2004; Lyman, 2002; Baker, et al., 1997; Shikora and Blackburn, 1997).

2.5.4 Psychosocial Complications

PN is a high-technology medical therapy that may require frequent hospitalizations and can turn patient's family life upside down, This complication can prevented by access of a nutrition support team (Baker, et al., 1997).

2.6 Parenteral Nutrition Preparation

A parenteral nutrition compounding process can be divided into four steps: receiving a PN order and reviewing its appropriateness; mixing substrates or base solutions that include amino acid, dextrose, and lipid; adding electrolytes and other additives to the base nutrient admixture; checking the final product. The PN admixtures can be compounded manually using a gravity transfer method or automatically using a computerized compounder. When compounding a PN solution, various issues need to be considered, for the example, concentration of available stock solutions and their chemical characteristics, mixing orders, chemical compatibilities and their stability in PN solutions, and storage of the admixture.

2.6.1 Parenteral Nutrition Components

2.6.1.1 Carbohydrate

Carbohydrate are provided as dextrose monohydrate, is the principal energy substrate in PN formulas, and it provides the primary fuel for the brain and bone marrow. This form of carbohydrate provided 3.4 kcal/g. The dextrose solutions are acidic, and pH ranges from 3.5 to 6.5 (Worthington,P., Gilbert,K.A., Wagner, B., 2000; Shikora and Blackburn, 1997). Commercially available concentration range from 3 % to 70 %. PN formulas that rely on glucose as a primary energy source are highly osmolar (Table 5).

Table 5 Approximate Osmolarity of Base Solutions and Additives of Parenteral Nutrition Admixture (Shikora and Blackburn, 1997)

Component	Osmolarity (mOsm)
Amino Acid	100 per %*
Dextrose	50 per %*
Lipid 10 %	2.8 per g
Lipid 20 %	1.5 per g
Lipid 30 %	1 per g
Calcium gluconate	1.4 per mEq
Magnesium (sulfate, gluconate)	1.7 per mEq
Potassium(acetate, chloride, phosphate)	2 per mEq
Sodium (acetate, chloride, phosphate)	2 per mEq

*final concentrations of Dextrose or Amino acid in the PN admixture

2.6.1.2 Protein

The primary function of protein in PN solutions is to maintain nitrogen balance and promote maintenance of lean body mass. They usually provide 15 - 20 % of total calories. Protein for parenteral administration is available as synthetic crystalline amino acid. The solutions contain a mix to essential and non-essential amino acids. Amino acid solutions can be broadly divided into two types; standard amino acid and modified (specialized) amino acid that include age–specific and disease–specific amino acid formulations. They are available in various bases such as 8.5 %, 10 % and 15 % solutions (Shikora and Blackburn, 1997).

2.6.1.3 Lipid

Intravenous fat emulsions supply lipids, which are a source of essential fatty acids (EFAs) and a concentrated source of calories. Intravenous lipid is isotonic and tolerated either by peripheral or central veins. Lipid emulsion contain soybean oil or a mixture of safflower and soy bean oils, with egg phospholipid added as an emulsifier, water, glycerin for adjust the osmolarity, and sodium hydroxide to adjust the pH. Lipid emulsion is available in concentrations at 10 %, 20% and 30%, providing 1.1, 2.0 and 3.0 kcal/ml respectively. Fats are a concentrated energy source providing 9 kcal/g (Worthington. et. al., 2000). IV fat emulsion can be administered

undiluted via a peripheral line, or mix as a 3-in-1 PN admixture for administration. Fat emulsion has pH ranges from 6 - 9 (Shikora and Blackburn, 1997).

2.6.1.4 Electrolytes

Electrolytes must be present in PN. They are essential nutrients that perform critical metabolic activities. Patients without significant fluid and electrolyte losses, hepatic or renal dysfunction, or acid-base abnormalities often do well with maintenance doses of electrolytes. Patients with gastrointestinal dysfunction including diarrhea, fistula output, and gastric losses often have impaired electrolyte homeostasis. Electrolyte additions to the PN solution reflect careful assessment of the clinical picture and the patient's individual needs (Worthington, et. al., 2000).

2.6.1.5 Vitamins

A vitamin is an organic substance occurring in minute quantities, which may be supplied in the diet or synthesized from essential dietary precursors. Vitamins are essential for specific metabolic functions to proceed normally and the body has variable stores of them. Vitamins should be added daily to the PN solution in order to prevent deficiencies. Parenteral vitamins are only stable for 24 hours after admixing.

2.6.1.6 Trace Elements

Trace elements are essential in small amounts for efficient substrate use and other supportive functions. Of the known essential trace elements, typical PN solutions contain zinc, chromium, copper, and manganese according to established guidelines. Silicon, cobalt, nickel, and vanadium are trace minerals vital to humans. Iron in PN solutions is limited because the potential for adverse reactions.

2.6.2 Mixing Order

The mixing sequence may be a critical factor affecting the compatibility of an admixture. The base solution, amino acid, dextrose and/or fat solution must be firstly mixed. The additives then are added by a mixing order. The only electrolytes for

which the mixing sequence seems critical are calcium and phosphate. These two ions readily combined to form a precipitate. It is recommended that phosphate must be added firstly and calcium be slowly added lastly in the mixing sequence with constant swirling. It has been suggested that instability substances, such as parenteral multivitamins, should be added just prior to administration of the nutrient solution. Finally, the admixtures should be periodically agitated and visually checked for precipitates during the mixing sequence and before delivered to the nursing unit (Grant, 1992; Shikora and Blackburn, 1997).

2.6.3 Labeling and Storage of Parenteral Admixtures

After final inspection, each bottle or bag is labeled clearly with the patient's name, ward, solution name, concentration, volume, additive amounts, formula letter, and bag number along with infusion rate. An expiration date of 24 hours is placed on each bag once additives have been injected. The solutions are refrigerated until used (Grant, 1992).

2.7 Parenteral Nutrition Compounding

In USP 30, PN solutions are classified in Medium-Risk Level Compounded Sterile Preparations (CSPs). They must be prepared in a manner that maintains sterility and minimizes the introduction of particulate matter. The safe preparation procedures can divide into the following main sections: environmental design, standard operating procedures, standardized process for PN.

2.7.1 The Environmental Design

2.7.1.1 Cleanroom and buffer area

Engineering control reduces the potential for airborne contamination in workspaces by limiting the amount and size of contaminants in the CSPs processing environment. Primary engineering controls are used and generally include laminar

airflow hood (LAFH), must provide at least ISO Class 5 quality of air to which sterile ingredients and components of CSP are directly exposed (Table 6, Table 7). Secondary engineering controls generally provide a buffer zone or buffer room as a core for the location of the workbenches. In general, the CSPs work environment is designed to have LAFH located in a buffer area. The class limit of the buffer or core room has to be demonstrably better than that of ambient air to reduce the risk of contaminants being blown, dragged, or otherwise introduce into the filtered unidirectional airflow environment (USP 31, 2008).

Buffer or cleanroom areas in which LAFH are located, should provide at least ISO Class 8 air quality. ISO Class 7 air quality is recommended to handle all eventualities (Table 6) (Buchanan, et al., 2002). This environment requires a positive–pressure differential, relative to adjacent less clean areas, of at least 0.05 in of water. Task carried out within the buffer area should be limited. Only the furniture, equipment, supplies, and other goods required for the tasks to be performed may be brought into this room, and they should be non-permeable, non shedding, and resistant to disinfectants. Cleanroom ceilings, walls, floors, fixtures, shelving, counters and cabinets in the buffer area should be resistant to sanitizing agents. Furthermore, junctures of ceilings to walls should be covered or caulked to avoid cracks and crevices where dirt can accumulate. If ceiling consist of inlaid panels, the panels should be impregnated with a polymer to render them impervious and hydrophobic. They should be caulked with an elastic sealant around the perimeter and clamped to the support flame. Walls may be of panels locked together and sealed or of epoxy-coated gypsum board. Preferably, floors are overlaid with wide sheet vinyl flooring with heat-welded seams and coving to the sidewall. Dust–collecting overhangs, such as ceiling utility pipes, or ledges, such as windowsills, should be avoided. The

exterior lens surface of ceiling lighting fixtures should be smooth, mounted flush, and sealed. Any other penetrations through the ceiling or walls should be sealed.

The buffer area should contain no sinks or floor drains. Work surface equipment, and furniture in the buffer area should be constructed of smooth, impervious materials, such as stainless steel or molded plastic, so that they are readily cleanable and sanitizable.

The High Efficiency Particulate Air (HEPA) filter in the ceiling air supply should be placed to avoid creating air currents inside the LAFH. Prefilters on the heating, ventilation, and air conditioning (HVAC) air blower should be changeable from outside the clean room (USP 31, 2008; Buchanan, et al., 2002).

2.7.1.2 Anteroom design

Access to the cleanroom should be via the anteroom door for personnel and an airlock pass through for most supplies. The anteroom provides a clean area for donning personnel barriers, such as hair covers, gloves, gowns, or full clean-room attire. Hand sanitizing and gowning activities also occur in the anteroom. Faucet handles are designed to be hands-free. Before processing CSPs, hands are resanitized after donning all appropriate garb, except for gloves. Compounding personnel must be capable of accessing the buffer area without use of their hands. Anteroom areas adjacent to buffer areas are intended to minimize the introduction of contaminants into buffer areas. The anteroom should meet ISO class 8 air quality (Table 6, Table 8).

Table 6 International Organization of Standardization (ISO) Classification of Particulate Matter in Room Air (USP 31, 2008)

Class Name		Particle Size	
ISO Class	**U.S. FS 209E**	**ISO, m^3**	**FS 209E, ft^3**
3	Class 1	35.2	1
4	Class 10	352	10
5	Class 100	3520	100
6	Class 1000	35,200	1000
7	Class 10,000	352,000	10,000
8	Class 100,000	3,520,000	100,000

Table 7 Environmental requirements for critical areas (ISO class 5)

Parameter	Requirement
Temperature	72 ± 5 °F
Relative humidity	30-50 %
Airflow	90 ft/min ± 20 %
Air quality	
Particulates	≤ 100 of ≥ 0.5 μm/cu ft
Microbial organisms	≤ 0.1/cu ft

Table 8 Environmental requirements for controlled areas (ISO class 8)

Parameter	Requirement
Temperature	72 ± 5 °F
Relative humidity	30-50 %
Air exchange	20/hr
Percentage fresh air	5-20%
Pressure differential	0.05 in of water
Air quality	
Particulates	≤ 100,000 of ≥ 0.5 μm/cu ft
Microbial organisms	≤ 2.5/cu ft

2.7.1.3 Laminar airflow hoods (LAFH)

A LAFH, either horizontal or vertical airflow is a cost effective, efficient way to provide ISO class 5 quality of air (Table 6) which required for pharmacy use. This hood includes a HEPA filter to retain airborne particles and microorganisms, and its use decreases the chance of product contamination (figure 1).

Uni-directional flow or laminar flow is the description given to mechanisms of particulate contamination removal where appropriate level of air moving at a velocity in the range o.3 to o.45 ms^{-1}, in a horizontal or vertical direction. Remove large particles by preventing them from settling onto any surface, there by systematically flushing them away from the working area. (Denyer and Baird, 2007).

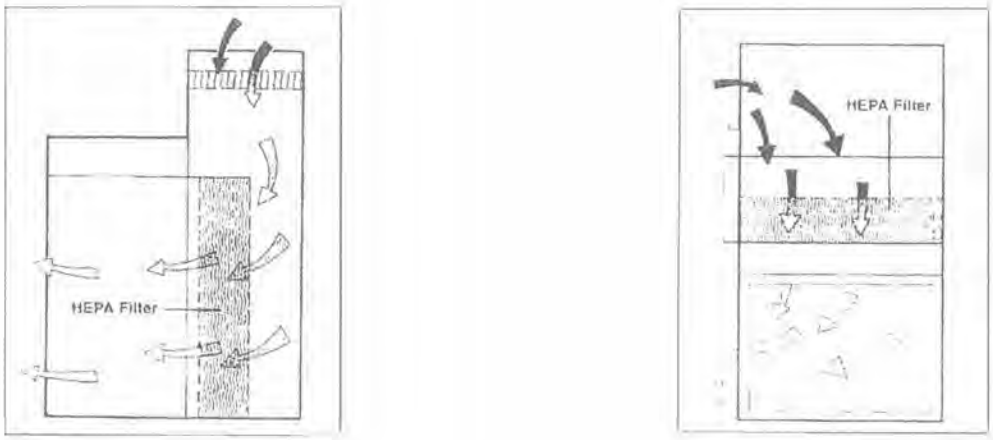

Figure 1 Horizontal laminar airflow hood (left) and vertical laminar air flow hood (right)

2.7.1.4 HEPA filters

A HEPA filter, is defined by its particle removal efficiency and its pressure drop at a rated airflow. A HEPA filter is defined as having a minimum efficiency in removing small particles (approximately equal to 0.3 μm) from air of 99.97 % (i.e. only three out of 10,000 particles, can penetrate through the filter) (Farguharson and Whyte, 1999).

The typical HEPA for pharmaceutical aseptic zones would have a flow-rate face velocity of 0.45 ms^{-1}. However, because any filter material subjected to a particulate load will eventually become clogged, Prefilters are used to remove the gross contamination found in untreated air in order to extend the useful life of the expensive final filters and minimize clean room downtime (Denyer and Baird, 2007).

2.7.2 Standard Operating Procedures (USP 31, 2008)

The pharmacy should have written properly approved standard operating procedures (SOPs) designed to ensure the quality of the environment in which a CSP is prepared. The following procedures are recommended:

(1) Access to the buffer or clean area is restricted to qualified personnel with specific responsibilities or assigned tasks in the area.

(2) All cartoned supplies are decontaminated in the anteroom area by removing them from shipping cartons and wiping or spraying with a disinfecting agent, such as sterile isopropyl alcohol (IPA), while being transferred to a clean, sanitized cart or other conveyance for introduction into the buffer or clean area. Individual pouched supplies need not be wiped because the pouches can be removed as these supplies are introduced into the buffer or clean area.

(3) Supplies required frequently or otherwise needed close at hand but not necessarily needed for the scheduled operations of the shift are decontaminated and stored on the shelving in the anteroom area.

(4) Carts used to bring supplies from the storeroom cannot be rolled beyond the demarcation line in the anteroom area, and carts used in the buffer or clean area cannot be rolled outward beyond the demarcation line unless cleaned and sanitized before returning.

(5) Generally, supplies required for the scheduled operations of the shift are prepared and brought into the buffer or clean area, preferably on one or more movable carts. Supplies that are required for back-up or general support of operations may be stored on the designated shelving in the buffer or clean area, but avoid excessive accumulation of supplies.

(6) Objects that shed particles cannot be brought into the buffer or clean area, including pencils, cardboard cartons, paper towels, and cotton items. Only nonshedding paper-related products (boxes, work records, and so forth) can be brought into the buffer or clean area.

(7) Traffic flow in and out of the buffer or clean area must be minimized.

(8) Personnel preparing to enter the buffer or clean area must remove all jewelry from hands and arms.

(9) Personnel entering the buffer or clean area must first scrub hands and arms with soap, including using a scrub brush on the fingers and nails. An air dryer or disposable nonshedding towels and used to dry hands and arms after washing.

(10) Personnel entering the buffer or clean area, after scrubbing, should don attire.

(11) No chewing gum, candy, or food items may be brought into the buffer or clean area or anteroom area.

(12) At the beginning of each compounding activity session, and after liquids are spilled, the surfaces of the direct compounding environment are first cleaned with purified water to remove water-soluble residues. Immediately thereafter, the same surfaces are sanitized with sterile 70 % isopropyl alcohol, or other effective antimicrobial agents, using a nonlinting wipe.

(13) When LAFH or barrier isolators are used as the ISO Class 5 air quality environment, their blowers must be operated continuously during compounding activity, including during interruptions of less than 8 hours. When the blower is turned off and before other personnel enter to perform compounding activities, only one person can enter the contiguous buffer area for the purposes of turning on the blower (for at least 30 minutes) and of sanitizing the work surfaces.

(14) Traffic in the compounding area is minimized and controlled. The compounding area is shielded from all less clean air currents that are of higher velocity than the clean laminar airflow.

(15) Supplies to be utilized in the compounding area for the planned procedures are accumulated and then decontaminated by wiping or spraying the outer surface with IPA or removing the outer wrap at the edge of the compounding area as the item is introduced into the aseptic work area.

(16) After proper introduction into the compounding area of supply items required for and limited to the assigned operations, they are so arranged that a clear, uninterrupted path of HEPA filtered air will bathe all critical sites at all times during the planned procedures. That is, no objects may be placed behind an exposed critical site in a horizontal position or above in the vertical laminar flow workbench.

(17) All supply items are arranged in the compounding area so as to reduce clutter and to provide maximum efficiency and order for the flow of work.

(18) All procedures are performed in a manner designed to minimize the risk of touch contamination. Gloves are sanitized with adequate frequency with an approved disinfectant.

(19) All rubber stoppers of vials and bottles and the neck of ampules are sanitized with IPA prior to the introduction of a needle or spike for the removal of product.

(20) After the preparation of every admixture, the contents of the container are thoroughly mixed and then inspected for the presence of particulate matter, evidence of incompatibility, or other defects.

(21) After procedures are completed, used syringes, bottles, vials, and other supplies are removed, but with a minimum of exit and re-entry into the compounding area to minimize the risk of introducing contamination into the aseptic workspace.

2.7.3 Standardized Process for Parenteral Nutrition (Kochevar et al., 2007)

A.S.P.E.N. advocates a standardized process for the delivery of PN. A standardized process addressed PN ordering, labeling, determination of nutrient requirements, screening of the PN order, administration, and monitoring.

2.7.3.1 Ordering PN

A.S.P.E.N. recommends that standardized order forms (or order entry screens) should be developed and designed for adult and pediatric PN formulations to aid prescribers in meeting the patient's estimated daily nutrition requirements and improve order clarity. The clinician and compounding pharmacist can assess the PN formulation to determine whether its contents are within an acceptable standard range according to the specific patient population (e.g. adult or pediatric). They shall also assess whether a clinical disease state or condition warrants a dose outside the standard range. Percent concentration in PN orders should not be used. The use of total daily dose is encouraged.

2.7.3.2 Labeling PN formulations

A.S.P.E.N. recommends the labels for PN formulations should be standardized and include the amount per day, the only column required on the label for the base formula, electrolyte additives, micronutrients, and medications. This supports the use of the 24-hour nutrient infusion system. Using the quantity per liter option in parentheses supports those programs that continue to admix PN in 1 liter volume.

2.7.3.3 Nutrient requirements

Determination of protein, calorie, fluid, electrolyte, vitamin, and trace elements components of a PN formulation should be based on standard nutrient requirements. The dose of each nutrient should fall within the accepted age-based standard range, except when warranted by specific clinical situations.

2.7.3.4 Screening the PN order

The calorie, protein, fluid, electrolyte, vitamin, trace element, and medication contents are reviewed for each and every PN prescription to assure that a complete and balanced nutrient formulation is provided. Balance is defined as the presence of the proper proportion of calories, protein, fluid, electrolytes, vitamins, and

trace elements to ensure adequate use by and assimilation into the body. Each of the PN components should be assessed for appropriateness of dose and for the potential of a compatibility or stability problem. Any dose of a nutrient outside a normal range, which is not explained by a specific patient condition or history, shall be questioned and clarified before the PN is compounded.

2.7.3.5 PN administration

Before PN administration, the patient's identity is verified and the PN label is reviewed for accuracy and expiration dates.

2.7.3.6 PN monitoring

All patients receiving PN should be monitored for complications and efficacy of nutrition support therapy.

2.8 Related Studies

PN formulations are susceptible to microbial growth because of their components such as amino acids and dextrose that can support fungal growth and fat emulsions that sustain bacteria and fungi (Opilla, 2008). Vonberg and Gastmeier (2006) found PN is one of the most critical products. In case of accidental contamination, they were associated with mortality rate close to 50%.

There are several reports of an outbreak of septicemia caused by contaminated PN. Llop et al (1993) reported an outbreak of sepsis related to contamination of TPN admixtures with *Staphylococcus saprophyticus*, a common environmental microorganism. In this occurrence, TPN admixtures prepared under laminar air flow hood (LAFH) located in the aseptic room of the TPN unit. They found that four of forty-five patients receiving the TPN admixtures showed clinical signs of sepsis, and ten of sixty-nine TPN admixtures from the TPN unit appeared positive in the microbiological control for *S. saprophyticus* along with positive cultures for *S.*

saprophyticus in tips, hubs and blood cultures of four patients. They attributed the idea of an outbreak caused by TPN contamination to an accidental breakdown of the aseptic elaboration procedure used in preparing the admixtures. Tresoldi et al. (2000) reported an outbreak of *Enterobacter cloacae* sepsis in a newborn unit caused by contaminated TPN solutions prepared under LAFH with aseptic techniques. They found that 11 high-risk newborns in the Neonatal Intensive Care Unit (NICU) were infected with *E. cloacae* and developed signs and symptoms of septic shock, which occurred in twelve to twenty-four hours after the initiation of PN. Despite of the prompt therapy with antibiotics, 7 newborns died suggesting that PN might be the source of nosocomial sepsis by *E. cloacae* in these neonates. Habsah et al. (2005) reported an outbreak of *Pantoea* spp. in NICU secondary to contaminated PN. They reported 8 babies developed sepsis. All the blood culture taken grew *Pantoea* spp. Sterility testing of the unused PN solutions and PN stock solution confirmed the *Pantoea* spp. contaminated. This evidence strongly suggested that contamination of PN solution may occurred during PN preparation in the pharmacy unit. In this outbreak, seven of eight affected neonates died, revealed a high fatality rate following an outbreak. Campos et al. (2007) reported an outbreak of *Enterobacter hormaechei* septicemia occurring in 6 NICUs of 5 hospitals in Brazil, caused by PN solution contaminated by this microorganism. The PN solutions all originated from the same manufacturer.

According to the septic complication due to the contaminated PN solutions, the source of contamination, such as the preparation environment, the aseptic technique processing must be investigated and validated to prevent repetitious contamination.