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A randomized controlled trial and cost effectiveness analysis of parenteral nutrition and enteral nutrition in severe pancreatitis: A model for health technology assessment.

by

Brian Edward Louie 

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Public Health

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Abstract

Decisions around the investment of resources, adoption and integration of innovations and new technologies into surgical practice are difficult. Health technology assessment is a systematic evaluation of a "health technology". It bridges a body of scientific inquiry with policy making to assist in technology decisions. In this thesis, the approach to and methods of health technology assessment are applied to a common surgical disease and its treatment. Acute pancreatitis is a reversible inflammatory state of the pancreas. Severe cases are treated with resting the pancreas, intravenous fluid therapy, general medical support and nutrition. The optimal choice of nutritional support is controversial; therefore, we conducted a randomized, controlled trial comparing parenteral with enteral nutrition. The results indicate both parenteral and enteral nutrition are safe and provide adequate nutrition. Enteral nutrition seems to attenuate pancreatic inflammation and is the dominant technology in terms of cost effectiveness. Using the HTA process, we concluded that enteral nutrition should be adopted, integrated and utilized.

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1.0 INTRODUCTION

Nearly a quarter century ago, Eiseman wrote, "the science and technology of surgical care has clearly outgrown society's ability to afford it".[1] He challenged future surgical leaders to consider the cost-effectiveness of their patient care decisions in light of technological growth and the ability to afford these new technologies. Today, the challenge remains the same, "How will we decide which innovations and new technologies are worth resource investment, adoption and integration into standard surgical practice?" Especially, when surgical innovation is only successful fifty percent of the time and only one in seven innovations results in a substantial improvement to patient care.[2]

Surgical care is heavily dependent on technology and its future success rests with emerging technologies that will improve the quality and quantity of life for patients.[3, 4] Yet, few current surgical technologies and practices have been rigorously evaluated to determine clinical effectiveness, or scrutinized in terms of cost for effect or benefit. In short, the evaluation of surgical technologies is rudimentary.

Recent trends in evidence-based medicine have highlighted the deficiencies in proper evaluation of existing and new technologies. The application and refinement of research methodologies, such as randomized controlled trials and observational studies to surgical practice are essential to increasing its knowledge base. More importantly, there must be a process to synthesize and organize the information and then to disseminate and apply this knowledge in such a way so as to inform decision-making. Health technology

assessment is a systematic method of evaluating a health technology that considers clinical outcomes data and economic implications and synthesizes the information to inform decision making from a variety of viewpoints. It has not been widely used to assess the surgical management of diseases or surgical interventions. However, the need for technology assessment is widely acknowledged.[5, 6] In this thesis, the approach to and methods of health technology assessment are applied to a common surgical disease and its treatment: acute pancreatitis.

Acute pancreatitis is a common reversible inflammatory state of the pancreas. In severe cases of this disease, treatment involves resting the pancreas from producing secretions for digestion, judicious intravenous fluid therapy, general medical support and nutrition. Total parenteral nutrition (TPN) is an intravenous form of nutrition that has been traditionally accepted as the preferred, if not the only, method to provide nutrition. However, this practice has evolved without rigorous assessment of the technology or its alternates. Total enteral nutrition (TEN) is a method of providing nutrition via the gut. It minimally stimulates the pancreas and is a technology that seems to be a feasible alternative to TPN in pancreatitis. [7-10]

We conducted a randomized, controlled trial comparing TPN with TEN in severe pancreatitis. The clinical value and cost-effectiveness of these types of nutrition were examined from both the regional health authority and individual physician perspective. The results and outcomes of the study represent the primary data of a health technology assessment. The evaluation of these modes of nutrition is further enhanced when these

results are coupled with data from similar studies. The goals were to provide evidence for the optimal management of nutrition in severe pancreatitis and to provide a plan to disseminate and integrate this technology assessment into the clinical practice of surgery.

2.0 HEALTH TECHNOLOGY ASSESSMENT AND SURGERY

Traditionally, improvements in surgical care were made by astute clinicians who adopted their own innovations and experimental successes based on careful observation. This method of evaluation, however, has a greater chance of choosing an unsuccessful or ineffectual technology.[2] The growing trend toward evidence-based medicine, where patient care decisions are influenced and directed by scientific evaluation of different treatment methods or technologies, has improved our chances of selecting beneficial technologies. But, surgeon investigators have been slow to adopt stronger clinical research methods to evaluate surgical technologies.

Even as evaluation methods are changed and refined, there remains a need for a more objective and comprehensive assessment of technology that serves to inform decision-making. Individual primary studies provide insufficient evidence alone. Systematic reviews or meta-analysis provide more comprehensive data and synthesis of results but fail to incorporate other tangible and intangible factors useful in decision-making. If decision making is to be influenced and changed by individual surgeons, by hospitals and by governments, there must be a systematic method of evaluation that incorporates more than just the clinical outcome and includes cost effectiveness data and a plan for dissemination.

Defining Health Technology Assessment

Health technology assessment (HTA) is a systematic evaluation of a "health technology", where health technology is broadly defined to include devices, equipment and supplies;

drugs; medical and surgical procedures; systems of care; support systems; and, organizational and managerial systems used in the prevention, diagnosis and treatment of disease in patients with ill health.[6, 11-14] Such systematic evaluation incorporates scientific evidence of the technology's efficacy, clinical effectiveness, cost-effectiveness and effect on quality of life. It can also be concerned with issues of equity and ethics. Decision-makers can then use this objective analysis to inform their decisions to purchase, promote, support, utilize or discard a particular technology.

HTA distinguishes itself from research by its multi-disciplinary nature and policy orientation that attempts to bridge a body of scientific inquiry with policy making. HTA can be accomplished by generating primary data through research studies or synthesizing information from secondary data sources such as existing databases and studies, but its strength lies in the dissemination and communication of information.[14] To bridge research and policy making, HTA is based on the interaction between four factors (Figure 2-1): 1) What specific question is being asked; 2) What perspective is being maintained; 3) Who desires the technology assessment; and, 4) Where is the technology in its life cycle.

All assessments begin with a specific question or goal that relates to a study population, an intervention/technology and an outcome. For example, a question may arise about the cost-effectiveness of screening mammograms for breast cancer in women aged 40 – 49.[15, 16] Or, a cancer program may request the purchase of Positron Emission Tomography (PET) scanner to detect metastatic cancer.

The perspective of the HTA is determined by the question being posed. Consider the first example of screening mammography. If women and interested cancer lobby groups request an evaluation of screening mammography, they will view screening mammography for identifying women aged 40 – 49 with breast cancer in terms of the success rate for identifying women at risk. A Ministry of Health will focus on the cost of a screening program and the additional costs of treatment. Whereas, with purchase of the PET Scanner, a hospital will consider the efficiency of the scanner at processing individuals and the cost of operation. Physicians will focus on the ability of the PET Scanner to detect metastatic disease.

At the present time, most HTAs are being performed by specialized HTA agencies or programs. These agencies are usually at arms length from government and hospitals. The Alberta Heritage Foundation for Medical Research and the former Conseil d'evaluation des technologies de la sante du Quebec[11] are examples of such agencies in Canada. More and more, hospitals are beginning to form HTA programs and physicians are beginning to have greater roles in HTA development.

The life cycle of a technology (Figure 2-2) traces the development of a particular technology in terms of utilization from innovation through to establishment and then extinction or obsolescence. HTA can be undertaken at any stage of the technology's life cycle. For each technology, an assessment can focus on one or more of the technology's attributes such as performance characteristics (eg. sensitivity and specificity), clinical

safety, efficacy, effectiveness and economic impact. Social, legal, ethical and political impacts can also be assessed. Assessments of emerging technologies are likely to focus on safety. Once safety is proven, assessments will focus on efficacy of the technology to ensure that the technology performs appropriately in clinical situations. Diagnostic and therapeutic modalities are likely to be assessed early in their life cycle because of developmental cost and impact on clinical practice. Mature technologies may be compared to new innovations in terms of effectiveness or economic impact as well as evaluated on "clinical, economic and social end points".[13] Extinct or obsolete technologies may be challenged against newer technologies in terms of safety, efficacy and economic efficiency.

The Practice of Health Technology Assessment

The mechanics of health technology assessment have been described in detail elsewhere.[12, 17] In brief, technology assessment resembles a research process or scientific method. (Figure 2-3) The process begins with a specific question being posed; a method of assessment is proposed; data is generated and collected to answer the question; the data is analyzed and synthesized; conclusions are reached and recommendations issued; finally, the results are disseminated and change is evaluated. Within these steps, there are four key considerations for most HTA: prioritization, data sources, evaluation and dissemination.

Within an organization or health system, there will be multiple technologies each with one or more specific questions, perspectives and stage of life. Determining which

technologies will be evaluated is the first step leading to assessment. For most organizations, strategic and capital plans, financial constraints and clinical necessity determine the priorities of HTA. Other organizations like the VA Hospitals have identified specific criteria to determine the relative priority of technology assessment.[12] These criteria can included the degree of morbidity and mortality; the incidence and/or prevalence of disease; the cost of disease and/or technology; variations in practice; and, the potential for improved health outcomes or reduced health risks. It is important to outline the process used to determine the order in which each technology will be assessed.

The next decision is whether to perform the analysis by generating primary data and information through an appropriately chosen study design in combination with other retrieved study data. Or, more commonly, to base the HTA on available quality studies identified through database review, interviews, reports and the Internet. Where high quality evidence exists (eg. multiple randomized controlled trials), it will be less costly to perform HTA using existing data. In the absence of strong studies or with only a few studies, a mixture of strategies may be employed such as a primary study in combination with existing studies.

Economic evaluation is a key component of HTA. More studies are collecting cost data and with the attention focussed on managing costs, there are more surgical studies that have integrated economic evaluation methods into the research protocols.[18, 19] However, most studies collect and present only rudimentary cost data. For HTA to be

comprehensive and effective, true economic evaluation is required in addition to or in parallel with the clinical research. Two components are required for economic evaluation: an assessment of costs and a determination of consequences. The specific details of economic evaluation have been previously presented elsewhere.[20]

An accurate assessment of all costs related to the technology and question being posed is required for proper evaluation. One of the challenges to having an accurate assessment is determining which costs should be included in the analysis. Several issues must be considered. Researchers must consider that the perspective of the evaluation will determine costs. For example, travel costs are a cost from the patient's and society's point of view, but not the government's.[20] Common costs between two programs being evaluated must be identified and can then be omitted because economic evaluation uses the difference between the costs of the two programs. Lastly, the magnitude of the costs must be considered in relation to the amount of effort and time taken to determine every input into a program.

Costs can be estimated by two means: 1) "bottom up" by quantities of resources and price/cost per unit of resources; thereby, producing marginal costs or the extra cost of producing an additional unit or, alternatively, "top down" by total resources divided by units produced; thereby producing an average cost. Marginal cost is preferred in economic evaluations because it allows for an examination of opportunity costs.

The consequences must also be appropriately determined. There are three types of consequences, which also define the type of economic evaluation. First, a cost-effectiveness analysis requires that the technologies being compared have a common outcome for evaluation. Mortality, life years gained and rate of complications are examples of such outcomes. Second, a cost-benefit analysis is utilized when no common outcome is available. The outcomes are converted into a common denominator, usually dollars. Third, a cost-utility analysis can be used when there are reservations or difficulties in valuing outcomes in dollars. Utility refers to the preferences individuals or society have for a particular set of health outcomes.[20]

The choice of evaluation can also be influenced by the position in the technology's life cycle and the availability of clinical studies. For example, early on competing technologies are evaluated on safety and efficacy. More mature technologies have often established a safety and efficacy record, but may produce varying quality of life. These situations can be assessed using utility measures rather than outcomes. Newer technologies may need to rely on intermediate or surrogate outcomes until the technology produces end outcomes sometimes years in the future. The evaluation can be revised when further analysis on the end outcomes becomes available.

Finally, the findings and recommendations must be formulated and then disseminated to a larger audience. After a period of time, expected changes must be monitored and systematically evaluated over time. Further findings and recommendations may arise out of this review and also require dissemination and implementation.

Surgical Technology Assessment

Health technology assessment in surgery is in its infancy, and the need for technology assessment in surgery is clearly evident.[6] Operating suites have numerous pieces of equipment, some of which are dusty and unused. Operating slates list various surgical procedures for the same diseases that have only been assessed by weaker study designs such as case series. Surgical patients also undergo laboratory testing, radiological evaluation and receive medical treatments that may have been evaluated for safety and efficacy separately, but have not been evaluated in terms of cost and policy decisions. Moreover, from hospital to hospital there is considerable geographic variation in surgical practice for similar conditions.[21, 22] With all of the variations in surgical practice and the lack of high quality evaluation, the way certain conditions are approached requires evaluation to promote clinical and cost effective methods of patient care while removing those that are ineffective and costly. [23]

Surgeons struggle with the idea of establishing a baseline or set of normative behaviors.[14] The practice of surgery is a unique interaction between surgeon, patient and disease or condition. Surgeons will validly point to uncertainties in diagnosis, differences in workmanship, judgement in decision making, training period and patient preference as reasons for variation in practice.[6, 24] However, the issues that must be addressed are the recognition of the need for evaluation, the timing and priority of evaluations, the interaction between surgeon and technology, knowledge of study design

including alternatives to randomized controlled trials and a wider scope of evaluative tools within each study area.

No surgeon disputes the need for evaluation. But, little progress has been made in the last 25 years with respect to the assessment of surgical technology. Multiple challenges have been issued to the surgical community to find a balance between technological growth and society's ability to fund health care. [1, 2, 4, 5, 25] Yet, since Eisman first issued the challenge in 1977, the technological growth in surgery has continued to follow a traditional approach. For example, laparoscopic surgery was adapted from gynecology to symptomatic gall bladder disease and before long the technology was wide spread and diffused without much formal evaluation.[6] Now it seems, that the growth in laparoscopic surgery is driven by innovative surgeons who want to be challenged by the possibilities rather than to question what role laparoscopic surgery should have in each disease state.

The timing of evaluation in surgery is crucial because with each new technology there is a learning curve between surgeon and technology. But, with the learning curve, there is also a small window of opportunity for evaluation before the technology fizzles or catches fire. Early laparoscopic cholecystectomy papers focused on safety concerns in terms of complications and recommended surgeons avoid cases of acute cholecystitis because of concerns with complications. However, some 15 years later, surgical skill has improved and no longer is acute cholecystitis a contraindication to laparoscopic surgery.

Unfortunately, the window for evaluation was so small that this technology emerged quickly and was ensconced rapidly.

The criteria outlined by Goodman et al[12] at the VA hospital for prioritizing technology assessments may be the best gauge for both timing and priority for evaluation. Early success with an innovation in a disease state with high prevalence that reduces mortality and morbidity or improves quality of life is likely to be quickly disseminated. For example, treatment of symptomatic cholelithiasis has been changed by laparoscopy and management of myopia has seen an explosion in laser surgery. Conversely, technologies related to disease with a lower prevalence with equivocal changes in morbidity, mortality or quality of life are likely to have a longer period for evaluation and dissemination is likely to more controlled.

Progression toward comprehensive health technology assessment has been hampered, first and foremost, by a lack of high quality scientific evidence demonstrating efficacy or effectiveness of the surgical technology.[6] The randomized controlled trial (RCT) represents the strongest experimental design and thus the most reliable evidence on which to base technology evaluation[26], yet over 50% of surgical "research" is comprised of retrospective studies involving single patient cohorts; that is, the descriptive case series and case reports which are the weakest experimental designs. [24, 27]. The randomized control trial in surgery accounts for only 2 - 9% of surgical research papers.[27] [28, 29]

An equally important issue within surgery is which research design is most appropriate to evaluate innovations and technology. Evaluation of surgical treatment by a randomized controlled trial was felt to be possible in only 40% of questions when the ideal situation was identified.[27] That leaves the majority of surgical questions to be evaluated by other research methods. Is the HTA process in surgery jeopardized without adequate numbers of randomized trials? Clearly, a comprehensive HTA should be based on more than several RCT studies. Are case control and cohort study designs valid to use within HTA? And, do case series and cross sectional studies provide any useable information?

When non-randomized studies are the only studies available, two situations will arise. Either, technology assessment proceeds with cautious interpretation, or it does not proceed. Using non-randomized studies within a HTA must be taken with a degree of confidence and the interpretation must be cautious. As a result, various parties will raise concerns about the quality of evidence used to make technological decisions. But, this will serve as an impetus to improve the quality of research design toward stronger experimental designs.

In a specialty that has developed new techniques and advanced its knowledge through observational methods, there must first be a commitment to advanced research techniques before HTA can be fully explored. With the exception of a few notable technological advances such as carotid endarterectomy, observational evidence must be used only to advance ideas for more substantial research comparison. Surgeons can easily move away from case series and introduce controls into their studies. This alone would enhance the

quality of research design significantly particularly in areas where RCTs cannot be administered.

Early comparisons of randomized trials and observational, non-randomized studies showed significant differences in results where observational studies inflated the positive treatment effect.[30, 31]. However, more recent studies comparing RCTs with observation studies that focused on studies after 1985 found that observational studies did not over estimate the treatment effect compared to RCTs.[32] A similar comparison of RCTs and observational studies identified through a search of meta-analysis papers found no over estimate of treatment effect by observational studies and yielded similar confidence intervals for both groups.[33] Both studies concluded that well designed observational studies (cohort or case control) do provide useful evidence and when used in a group of similar studies can inform decision-making; however, these must be still approached with caution.

Meta-analysis and non-quantitative systematic reviews represent newer research methods that can also be used for HTA. Meta-analysis is a statistical method that combines a series of smaller studies in an attempt to overcome the low power associated with small sample sizes. Systematic review attempts to draw conclusions about a clinical question by reviewing all available literature, but without the statistical support. Meta-analysis must also be viewed cautiously. Specific attention should be directed at the studies included in the meta-analysis because the quality of studies included is directly related to the quality of the information coming out of a meta-analysis. For example, a recent

comparison of meta-analyses and large randomized controlled trials found that meta-analysis that did not include RCTs recommended ineffectual treatment in one-third of cases and rejected useful treatment in a third of cases.[34]

For HTA to be useful and comprehensive in surgical practice, several changes must occur. First, surgical research needs to involve a mixture of research strategies that involve not only randomized controlled trials and case series, but also begin to incorporate observational studies. Second, its research must also widen its focus from safety and efficacy, morbidity or mortality to include aspects of economic evaluation [18, 19] and quality of life assessment.

Even with these changes, the future success of HTA and surgical research depends on dissemination of findings and evaluation of change. This will require additional research into the methods, such as qualitative methods[35], by which surgeons continue to learn and adapt their knowledge and skills after residency training. Dissemination of successful technology evaluation and of successful surgical research will require more than just publication in surgical journals, interaction at conferences and directed teaching sessions.[36] There is a certain reluctance to alter tried and true methods until an unpleasant experience occurs with that tried and true method. This may represent a "teachable" moment for surgeons that can be exploited.

There is a need to undertake a comprehensive evaluation of surgical technologies in today's health care environment. Surgery remains a unique setting in which the craft of

surgery is passed on in an apprenticeship, and innovations and experiments are treated in a similar fashion. With changes to surgical research methodologies, health technology assessment can help surgeons to make decisions about surgical care, identify and promote successful and economically sound surgical treatments.

3.0 ACUTE PANCREATITIS

Acute pancreatitis (pancreatitis) is an inflammatory state of the pancreas that has "numerous etiologies, an obscure pathogenesis, few effective remedies and, often, an unpredictable outcome".[37] It is a common disease with an increasing incidence that ranges as high as 38 per 100 000 population.[38-40] Morbidity and mortality from this disease have fallen to less than 10% over the last quarter century, but remain high because of the multiple etiologies, complex pathogenesis and lack of effective treatments.[41] [42] Improvements in these rates can be credited to advances in critical care medicine, conservative treatment pathways that avoided early surgical intervention and the development of endoscopic retrograde cholangiopancreatography treatments for gallstones.

Etiology and Pathophysiology

There is a myriad of etiologic factors (Figure 3-1) that have been associated with the development of acute pancreatitis. It is believed that acute pancreatitis is caused by auto-digestion of the gland by activation of pancreatic enzymes within the substance of the gland. The common inciting event leading to auto-digestion is pancreatic duct occlusion. The specific mechanisms by which gallstones and alcohol have been investigated, but other etiologies such as medications, pancreatic divisum, hypercalcemia, etc have a less clear relationship with the development of pancreatitis.

Gallstones and "biliary sludge" were identified as causing mostly transient obstruction at the Ampulla of Vater.[43-45] Alcohol ingestion was thought to cause changes in

pancreatic exocrine secretion leading to precipitation of protein with the ducts causing obstruction.[46]. However, recent animal studies suggest that alcohol damages muscarinic receptors in the pancreas, sphincter of Oddi and duodenum causing a hypersensitivity to acetylcholine. Acetylcholine produces a release of protein-rich pancreatic juice, which creates a hypertonic duodenal state leading to duodenopancreatic reflux and acute pancreatitis.[47]

Obstruction of the pancreatic duct alone does not lead to pancreatitis, nor does enzyme secretion because most pancreatic enzymes are secreted as inactive zymogens. Steer[48] showed that digestive enzyme synthesis continues during the early phases of pancreatitis, but there is an abnormal accumulation of enzymes because secretion is blocked and enzymes accumulate within the gland. In normal pancreatic function, the digestive enzymes are segregated from lysosomal enzymes, but in pancreatitis the digestive enzymes are co-located in fragile vacuoles with the lysosomal hydrolase: cathepsin B. As these vacuoles become more fragile, trypsinogen is activated which further activates other zymogens. The release of trypsin into the cytoplasm of acinar cells causes injury and likely also activates other zymogens further propagating cell injury. (Figure 3-2)

Steer[48] and Saluja and Steer[49] hypothesized that after acinar cell injury occurred there must be another process that influenced the severity of pancreatitis. Together they showed that severe acinar cell injury can initiate a systemic inflammatory response syndrome, which leads to severe pancreatitis. The cytokines, IL-1 and TNF-α, which are produced by infiltrating macrophages and PMN's, are the key mediators leading to multi-

organ dysfunction.[50-52] TNF-α is produced by infiltrating macrophages within the pancreas in response to acinar cell injury. Systemic response to TNF-α is shock. IL-1 is a proinflammatory cytokine that is derived from macrophages and activates neutrophils, induces up-regulation of adhesion molecules and induces a shock-like state. Platelet activating factor also has a central role in the development of SIRS[50] by altering vascular tone, which results in hypotension, vascular permeability, capillary leakage and platelet and neutrophil aggregation.

Diagnosis of Pancreatitis

A diagnosis of pancreatitis is made with a combination of clinical, biochemical and radiological findings. The initial clinical presentation is of sudden onset upper mid-abdominal pain that is steady and often radiates directly through to the back. The pain peaks over several hours and can remain for hours to days after onset. Typically, patients associate the onset of pain with eating or alcohol ingestion. Nausea and vomiting commonly follow the onset of pain.

In the majority of patients with this clinical picture, biochemical evidence of pancreatic enzyme release is present with elevated serum lipase or amylase. A serum amylase four times normal or a lipase twice the upper limit of normal are consistent with a diagnosis of pancreatitis.

Radiologic investigations are frequently used to rule out other causes of abdominal pain rather than to diagnose pancreatitis. Abdominal radiographs help to rule out other causes

of upper abdominal pain. Subtle radiologic finding such as a sentinel bowel loop and calcifications in the area of the pancreas may point the clinician in the direction of pancreatitis. Frequently, ultrasound examination will be obtained to identify gallstones as a potential etiological factor and to provide gross examination of the pancreas. In up to 50% of cases, ultrasound cannot be used to diagnose pancreatitis. Computed tomography is an excellent modality for diagnosis pancreatitis, but is mainly used to provide information about the severity of the disease process and its complications.

Natural History of Pancreatitis

The natural history of acute pancreatitis is characterized by "time-dependent stages with specific morphologic and clinical patterns.[53] (Figure 3-3) With the onset of symptoms, it is not possible to predict which pathway a patient will take. However, over the next 24 - 72 hours, patients will "declare" themselves into one of two groups. Approximately 75% of patients with acute pancreatitis will have mild disease, minimal organ dysfunction and an uncomplicated resolution of the disease. The remainder will follow a longer, more protracted and complicated course. This group of patients will experience more organ dysfunction, require greater medical resources for support and be more susceptible to infectious complications.

Death in this group of severe acute pancreatitis occurs in two groups. Early deaths occur within the first week and are related to complications arising from multi-organ dysfunction (MODS) and systemic inflammatory response syndrome (SIRS).[53] These patients develop an exaggerated inflammatory response with concomitant organ

dysfunction that leads to death. Late deaths (> 2 weeks) are usually a result of a second event after surviving the initial clinical course. Local and systemic septic events are common inciting events that re-establish the inflammatory response and lead to organ dysfunction and death.[53, 54]

Organ Dysfunction with Pancreatitis

The development of organ dysfunction in severe pancreatitis is frequent and is seen in 25 - 50% of patients especially in patients with advanced age and chronic diseases.[55, 56] Accordingly, mortality is increased with the development of organ dysfunction and approaches 80% in some studies.[55, 57]

The cardiovascular system is the most frequently affected system and has the highest associated risk.[55] Hypotension and shock are attributed to intravascular fluid losses, through increased vascular permeability and fluid sequestration. Circulating cytokines also play a significant role in the development of shock and hypotension.[57] Studies of hemodynamics in severe pancreatitis have demonstrated a physiologic state similar to sepsis with a tachycardia, high cardiac index and output and low systemic vascular resistance despite elevated central venous pressure and pulmonary capillary wedge pressures.[57, 58]

The development of respiratory failure seems to be decreasing and contributing less to mortality. Mild respiratory failure can be seen with pleural effusions, hypoxia, atelectasis and pulmonary edema, which are due to the abdominal pain and vascular permeability.

More severe respiratory failure involves the development of pneumonia and/or adult respiratory distress syndrome through the release of phospholipase A_2 , which degrades pulmonary surfactant.[37]

Gastrointestinal failure in severe pancreatitis has been identified as a probable source of sepsis through bacterial translocation secondary to gut permeability. In fact, in one study, gut failure was associated with the highest mortality rates.[59] Several animal studies showed increased gut permeability as evidenced by culture positive lymph nodes[60], higher bacterial counts within and across the cecum and duodenum[60-62] and by translocation of labeled markers from within bowel lumen.[63, 64]. Confirmation of bacterial translocations in human studies is difficult to obtain and is usually measured by proxy outcomes, such as septic events, rather than direct measurement.[65] No human study has been able to prove that bacterial translocation via the gut is responsible for the septic complications in severe pancreatitis.

Other organ systems are also prone to failure. Renal and hepatic failure are prevalent and are usually related to the development of shock and hypotension. Exocrine pancreatic function is not altered during episodes of acute pancreatitis and continues to produce secretions at a normal rate.[66] The hypocalcemia found with acute pancreatitis is, in part, due to an inadequate parathyroid response.[67]

Classification, Severity Stratification and Prognostic Systems

Acute pancreatitis is a difficult disease to classify because it presents many different clinical pictures to physicians. The first classification system was developed in Marseilles in 1963 at the first international pancreatitis conference.[68] Since that time, research and clinical observation have caused the original histopathological classification system to evolve to an entirely clinical system in 1984[69] and finally to a morphological and clinical system in Ulm, Germany in 1991.[70, 71]

Acute pancreatitis is classified into four major categories[53]: 1) acute interstitial edematous pancreatitis, 2) acute necrotizing pancreatitis with sterile or infected necrosis, 3) pancreatic pseudocyst, and 4) pancreatic abscess. This concurred with many clinical observations that recognized that the majority of patients (75-85%) presented with the mild form of the disease, which tends to have a short and self-limiting course – acute interstitial edematous pancreatitis. And, in 10-25% of patients, the pancreatitis was more severe, protracted, potentially life threatening and complicated by sterile necrosis, infected necrosis, pseudocyst formation and abscess.

The goal, now, is to find a system or test that will predict whether patient will develop the severe form of pancreatitis. A multitude of severity stratification and prognostic systems have been developed, before and after this classification system was developed, in an attempt to predict prognosis and/or establish disease severity. Clinical assessment of severity in pancreatitis is unreliable and the goal is still to predict who will have severe pancreatitis.[70] Identification of these patients would allow streaming to critical care or

specialized care units and allow clinicians to start treatments designed at arresting the pathophysiologic process. These systems can be grouped into 3 categories: 1) biochemical, 2) clinico-biochemical and 3) single factor.

The biochemical stratification systems are most well known and include Ranson's criteria and Imrie's classification. Ranson was the first to evaluate the prognostic factors of acute pancreatitis and to develop a system for assessing prognosis. In Ranson's original work, he studied mostly alcoholic pancreatitis in an attempt "to assess methods for the early identification of patients with severe pancreatitis and to evaluate further the role of early operative intervention".[72, 73] Forty-three objective findings were gathered from over the first forty-eight hours after admission. Eleven findings were significant for predicted morbidity and mortality. He concluded that three or more these signs were associated with a 62% chance of death.[74]

Imrie et al[75], suggested a modification to Ranson's criteria that included 9 biochemical criteria measured over a 48 hours period from the time of admission. This system was then revised down to 8 biochemical markers.[76, 77] Imrie's original criteria were able to predict the death of patients in his original research. Subsequent modifications have correctly predicted severity in approximately 80% of cases.

A variety of clinical and biochemical based systems have been used to evaluate the severity and prognosis of acute pancreatitis.[78-82] APACHE II is most commonly used and has been validated in a large series of critically ill patients.[83] This system is

designed to objectively measure the degree of acute illness by accumulating data on 34 variables within 32 hours of admission. In addition, the patient's pre-morbid health status is considered in the overall score. APACHE has been utilized in multiple settings including acute pancreatitis.[78, 79] Not only does it correlate well with mortality, but after 48 hours APACHE II accurately predicted outcome in 88% of attacks.[79]

In addition to these complex and multi-factor scoring systems, researchers have continued to look for a single factor test that could predict the severity and outcome of acute pancreatitis. C-reactive protein (CRP), when used serially, has been shown to differentiate between mild and severe attacks of acute pancreatitis[84], but not within 48 hours of admission.[85] More severe cases had higher and more persistent levels of CRP compared to milder cases. CRP has also been used to predict the presence of pancreatic necrosis but without significant success. Peak concentrations of CRP > 209 mg/L on the second, third or fourth day of disease and > 119 mg/L at the end of 7 days were shown to be most discriminative.[86]

Recent research has focused on the value of cytokines (eg. IL-6) and proteins associated with acute pancreatitis as predictors of severity. Cytokines[87-91], trypsinogen activation peptides[92-94] and pancreatitis-associated protein[95] have all been shown to be useful parameters for the early prediction of the prognosis of acute pancreatitis. However, these tests are not widely available, are costly and are best served within a research setting at present.

Computed tomography (CT) has also been used to grade and assess pancreatitis and has been well correlated with both Ranson's criteria and APACHE II scores.[96-99] Only one study found that a biochemical scoring system was not enhanced with the use of CT .[100]

Comparisons have been made of all of the severity stratification and prognostic systems. The results are inconsistent. Limitations exist for each and every system. Ranson and Imrie offer simple biochemical systems that can be determined by 48 hours, but have less predictive ability. In combination with CRP that predictive ability is greater than 80%.[101] However, neither of these systems has been validated for serial use. APACHE and CRP have both been shown to be useful in serial measurements. The difficulty with APACHE and the other biochemical systems is that physicians must remember to order all of the investigations at the outset. Frequently, less common and more invasive tests such as LDH and arterial blood gases are omitted; thus, limiting the usefulness of the system. A mixture of strategies that include CRP, APACHE and CT is best employed in attempting to stratify and prognosticate patients with acute pancreatitis.

Management of Acute Pancreatitis

The management of pancreatitis varies with the severity and etiologic agent of pancreatitis but is based on a platform of conservative and supportive measures for all patients with pancreatitis. The initial treatment for all patients with pancreatitis regardless of severity and etiology is to discontinue oral intake to minimize pancreatic stimulation and institute supportive measures including judicious intravenous fluids,

analgesia and anti-nauseants.[102, 103] Additional adjunctive measures might include nasogastric suction for ileus or prolonged vomiting and indwelling urinary catheter for fluid management.

The ongoing management of pancreatitis (Figure 3-4) involves a search for the etiologic agent, an assessment of severity and clinical reassessment. Subsequent treatment is devised to address the etiologic agent, to manage the severity and to treat complications of pancreatitis. Irrespective of these ongoing processes, resumption of oral intake and discontinuance of supportive measures occurs as patients clinically improve and pancreatic pain has resolved.[104]

The search for an etiology of the pancreatitis must be thorough in order to devise appropriate treatment. In spite of this search, idiopathic pancreatitis has been reported as high as 30% in some series, but has been found to be related to microlithiasis.[105, 106] An efficient search will include a complete history followed by biochemical and radiological tests. Historical factors should elicit the amount and frequency of alcohol intake as well as current medications. Biochemical testing should not only ensure proper severity stratification but also suggest the presence of gallstones by elevated alkaline phosphatase, amino transaminases and bilirubins or lipid as an etiology by elevated triglycerides and cholesterols. Ultrasound evidence of acute gallstone pancreatitis or choledocholithiasis (dilated common bile duct, stones in the duct) will suffice for most patients. Where there are recurrent attacks or historical factors suggestive of malignancy,

ERCP, CT or MR scanning should be considered to look for evidence of ductal obstruction such as pancreatic divisum or malignancy.

The cornerstone of management of mild pancreatitis is judicious intravenous fluid administration and ongoing monitoring. The treatment remains supportive as described above. Once the search for an etiologic agent has identified a cause, then further therapy is directed at that cause once the pancreatitis has settled. Oral intake is resumed as the patient's pain resolves and clinically improves.

The management of severe pancreatitis is often more complex and involved. In addition to the general supportive measures, patients may require admission to intensive care unit or specialized care units depending on the degree of organ failure. In these situations, central venous pressure monitoring, swan-ganz catheter assessment, nasogastric suction, indwelling urinary catheter, ventilatory support and supplemental nutrition may all be required. After stabilization and advanced severity assessment, specific treatment depends on the etiology and complications that arise.

Management of Specific Etiologies and Complications

In addition to the supportive care afforded to all patients with pancreatitis regardless of the etiology of their pancreatitis, there are several situations in which specific therapies are devoted to certain etiologies. Moreover, there are also therapies designed for the complications of pancreatitis.

The management of severe gallstone related pancreatitis has been revolutionized by the development of ERCP and sphincterotomy. Early studies showed that ERCP and sphincterotomy early in the course of gallstone pancreatitis reduced morbidity presumably from reducing biliary sepsis.[107] [108] However, in the majority of cases, the gallstones had passed by the time of the ERCP and the complications of ERCP which can be greater than 10% in this acute situation may in fact be worse. Folsch et al[109] showed that early ERCP and sphincterotomy had no benefit on patients with gallstone pancreatitis except those with biliary obstruction or biliary sepsis. For patients with severe gallstone pancreatitis who show signs of clinical deterioration as evidenced by worsening biliary enzymes and cholangitis early ERCP and sphincterotomy are required for treatment.

In severe pancreatitis, a CT scan can be obtained to further determine the severity of pancreatitis. The role of CT scan early in the treatment of pancreatitis has not proven to change outcome, but has been used by clinicians to rule out other sources of intra-abdominal catastrophe that could not be excluded clinically and to assess the pancreatitis to distinguish between interstitial and necrotizing pancreatitis. In this setting, contrast enhanced CT will accurately identify necrosis over 90% of the time.

In patients where interstitial pancreatitis is identified the current supportive management is continued until resolution. However, in the presence of necrotizing pancreatitis, patients are treated based upon the clinical course. Patients with pancreatic necrosis who are improving clinically and have organ dysfunction that is resolving require continued

medical treatment and support. Patients whom are deteriorating and have worsening organ dysfunction are likely to have infected pancreatic necrosis as opposed to sterile necrosis.

There are two methods to manage potentially infected necrosis.[110, 111] Percutaneous needle aspiration by ultrasound or CT guidance has been suggested as a method for proving infected necrosis. If infection is proven, then surgical debridement is warranted. The use of percutaneous drainage methods and antibiotics alone is not supported in the literature. Alternatively, some clinicians argue that in the situation of worsening organ dysfunction with a CT suggestive of infected necrosis that surgical debridement is warranted without the step of proving infection which may take 24 – 48 hours for culture results. Whether it is infection or sterile necrosis that is driving the worsening clinical picture is irrelevant. Debridement of both infected and sterile necrosis is likely to reduce the inflammatory mediators allowing resolution of organ dysfunction.[112-114]

The use of antibiotics in severe pancreatitis is controversial. Most papers agree that mild pancreatitis does not require antibiotic coverage. In severe pancreatitis, the use of antibiotics is less clear. Reports of early randomized trials recommended the use of Imipenem™ with necrotizing pancreatitis and showed a reduction in the development of pancreatic sepsis.[115, 116] However, they failed to show a difference in the key outcome indicator of mortality.[115] A recent meta-analysis and systematic review[117] of antibiotic use in severe pancreatitis showed a reduction in sepsis of 21% and mortality 12.3% with small numbers need to treat.[118]

Octreotide is a synthetic somatostatin analogue, which inhibits exocrine pancreatic secretion. Given that "autodigestion" was a key component of the theory of pancreatitis, several studies were designed to assess the use of octreotide in pancreatitis. Although early trials showed small reductions in mortality, recent papers did not show any benefit to octreotide in pancreatitis.[119, 120]

Further research was then directed at agents that altered the inflammatory cascade mediators as the pathophysiology of pancreatitis became elucidated. Platelet activating factor (PAF) is stored in cells as an inactive precursor linked to cell membranes. Activation of phospholipase A2 causes PAF to be synthesized and secreted. PAF has a key role in the development of pancreatitis through control of exocrine secretion. Lexipafant is a PAF antagonist that in animal studies was shown to reduce the morphological damage as well as ameliorating the acute lung injury associated with pancreatitis. Despite promising animal trials, Phase II and III trials failed to show a benefit to giving lexipafant in acute pancreatitis.[121, 122] Current research efforts continue to focus on modulating the various mediators of the inflammatory cascade such as TNF and IL-6.[123]

Acute pancreatitis is a complex and multifaceted disease. Most patients experience a mild form of the disease and have an uncomplicated resolution. A small percentage of patients experience a more severe form of the disease that is mediated by cytokines and the inflammatory cascade. Because of the multiple etiologies and wide variance in

clinical appearance, attempts at stratification and prognosis have only been able to predict the severe form and its complications approximately 80% of the time. Treatment has been directed at supportive therapies. Specific etiologies and complications are treated with appropriate endoscopic or surgical intervention. Newer strategies aimed at the inflammatory cascade have not proven beneficial largely due to the extent of the cascade.

4.0 NUTRITIONAL SUPPORT

A traditional surgical and medical principle or "dogma" in the management of patients with acute pancreatitis is "Nothing per os" (NPO). Theoretically, this would "rest the pancreas" by avoiding stimulation and production of pancreatic digestive enzymes and thus minimizing auto-digestion of the gland. This principle has no significant impact on the nutritional status of patients with mild pancreatitis because these patients usually resume oral intake with seven days.[124] However, patients with severe pancreatitis are frequently hypermetabolic, have a systemic inflammatory response syndrome and have multi-organ dysfunction and are potentially without nutrition for longer than seven days. This frequently results in marasmus, a combination of protein and caloric malnutrition that is characterized by a global deficiency in lean body mass, fat reserves and visceral protein. Therefore, patients with severe pancreatitis who are NPO for greater than 7 days will require nutritional support as part of treatment for pancreatitis.

The optimal route of nutrition support in acute pancreatitis is controversial. Historically, patients were fasted. With the development of parenteral nutrition in the early 1970's, a method to rest the pancreas and provide nutrition simultaneously was created. However, the true value of nutritional support was not suspected until Feller[125] reported a reduction in mortality in pancreatitis patients given TPN and concluded that nutrition played a significant role in reducing complication and mortality. Critics of parenteral nutrition have upheld the view that TPN is not a panacea.[126] Studies from the trauma and burn literature have created a resurgence in the interest of enteral nutrition because of reductions in septic complications seen in patients who were supported enterally in

comparison to those supported parenterally.[65] Newer studies have shown that enteral nutrition is tolerated in acute pancreatitis and therefore, may be a suitable alternative to TPN.

Metabolism in Severe Pancreatitis

Even though the hemodynamic patterns in pancreatitis are similar to those seen in sepsis and the increased oxygen consumption is a sign of hypermetabolism, there is inconsistent evidence that severe pancreatitis is a hypermetabolic state. Studies comparing the Harris-Benedict equation (an equation used to estimate energy expenditure based on sex, weight, height, age and an adjustment factor for stress levels) and indirect calorimetry show considerable variability in resting energy expenditure levels.[127] It is clear that Harris-Benedict predictions are unreliable estimates of energy expenditure. Furthermore, even with established sepsis, the energy expenditure is not clearly different from the expenditure in non-septic patients.[128] These findings are not surprising given the clinical variability of the disease. Further research will be required to determine the state of metabolism in severe pancreatitis.

Nutritional Care Plan

Decisions to initiate nutritional support in patients with acute pancreatitis are based on several factors including pre-morbid nutritional history, severity of pancreatitis, pain and likelihood of tolerating oral intake. Regardless of the route of delivery, nutrition support should be provided only after careful assessment and determination of nutritional needs in a patient who is at nutritional risk.

The patient's energy requirements are estimated using one of several methods in order to determine how much nutrition should be delivered. The Harris-Benedict equation (HBE) frequently underestimates the required energy levels despite being modified for patient stressors. Another formula, which is useful for estimating energy expenditure, is to provide 25 - 30 kcal/kg of lean body weight. Indirect calorimetry is the most accurate method of determining resting energy expenditure levels. Unfortunately, this requires an indirect calorimeter and skilled personnel. In our institution, indirect calorimetry is reserved for patients on long-term nutritional support (greater than 7 days) or for patients who have energy estimates that are prone to error because of severe malnourishment or potential for significant changes in energy expenditure.

Three sources of energy are available for use by the patient: carbohydrates, protein and fat. When given parenterally, these energy substrates may be associated with metabolic complications. Carbohydrates are the primary source of non-protein calories in parenteral nutrition. The delivery of dextrose via central venous catheter is associated with hyperinsulinemia and hyperglycemia. TPN-induced liver dysfunction may also be due in part to high rates of dextrose infusion. Rapid muscle wasting occurs secondary to increased amino acid oxidation and gluconeogenesis. 1.5 g/kg/day of protein is usually adequate to obviate the catabolic mediated protein losses. Patients with impaired renal dysfunction or hepatic encephalopathy may require an initial protein intake of 0.6 – 1.0 g/kg/day. Enteral or parenteral lipid substrates may have significant implications for acute pancreatitis. Enterally, fat stimulates CCK secretion, which in turn simulates

pancreatic protein secretion. Parenterally, fat emulsions have been reported to induce pancreatitis when triglyceride levels are greater than 20 times normal.

Measures of Nutritional Status

After institution of nutritional support, ongoing monitoring and management must determine if enough calories and protein are being provided to support bodily functions. Nutritional investigations can be grouped into three categories: anthropometric measurements, serum proteins and tests of immune function. Practically, anthropometric measurements and tests of immune function are difficult to use at the bedside. This compounded by significant volume changes in critically ill patients and difficulty getting accurate patient weights. Bedside tests of immune function such as delayed hypersensitivity skin testing can be predictive of malnutrition but do not change management.

The serum proteins, albumin, transferrin and pre-albumin, are simple to obtain, use and interpret. They are widely used for assessment of nutritional status and are supposed to reflect visceral protein stores. In infectious and inflammatory disease states, the liver decreases production of all three serum proteins while increasing acute phase reactants such as C-reactive protein. In non-complicated disease states, the balance of production by the liver returns to normal. Albumin is a serum protein with a half life of 20 days. Its metabolism is complex and influenced by many factors. As such, it is a poor indicator of changes in nutritional status.[129] Transferrin is a beta-globulin protein that transports

iron and has also been shown to be useful in documenting protein-calorie malnutrition but is poor marker of nutritional status.

Pre-albumin is a serum protein with a short half-life and has been shown to be responsive to changes in dietary protein and energy levels. Serum levels respond rapidly to re-feeding and therefore could be used to detect sub-clinical malnutrition and monitor the effectiveness of dietary intervention.[129] Pre-albumin levels drawn prior to initiation of nutrition and after seven days were shown to correlate with urinary nitrogen balance.[130]

The twenty-four hour urinary nitrogen balance is a simple estimate of protein synthesis or breakdown. Negative nitrogen balance suggests ongoing protein catabolism. Conversely, a positive nitrogen balance suggests that protein losses have been limited or stopped.

Indirect calorimetry is the most accurate method of determining energy expenditure by measurement of oxygen consumption and carbon dioxide production. While not a true measure of nutritional status, it can be used to determine whether enough calories are being provided to severely ill patients. In addition, the respiratory quotient is calculated and can be used to interpret how the body is utilizing various fuel sources.

Routes of Nutritional Support

When patients with acute pancreatitis are fasted, two primary routes of nutritional support, parenteral and enteral, are utilized. Parenteral nutrition is usually delivered into the central venous system by means of a central venous catheter. Occasionally, it can be provided through a peripheral vein for a short period of time. All three sources of energy are easily delivered in this manner.

Enteral nutrition can be delivered by mouth, but is usually delivered by a small bore tube placed into the upper gastrointestinal system via the nasal passage. These tubes can be placed into the stomach or into the small bowel either by a gastroscope or under radiologic guidance. All three sources of energy are easily delivered in this manner.

Total Parenteral Nutrition

Parenteral nutrition was developed in the late 1960's and has been widely used since the early 1970's to provide nutritional support in acute pancreatitis because it supports the concept of pancreatic rest[131], is easily provided and bypasses the problem of ileus found in many pancreatitis patients. It has been studied extensively with uncontrolled and controlled research designs and the results focus on four issues: pancreatic stimulation, nutritional impact, disease outcome and catheter-related sepsis.

Multiple studies have been undertaken to determine the effect of parenteral nutrition on pancreatic exocrine secretion, but the results of both animal and human studies have been

inconclusive. Canine studies comparing oral, intraduodenal and intravenous hyperalimentation produced significant pancreatic stimulation in all three arms. However, the intravenous arm produced the least amount of stimulus as measured by volume of pancreatic juice and protein secretion.[132] Further studies also showed that intravenous amino acids and lipid provoked a dose-dependent rise in pancreatic protein and a rise in CCK.[133] More recent research has contradicted earlier findings by showing no increase in pancreatic secretions, protein or serum CCK levels.[134] Finally, two studies of healthy humans showed only minor effects on pancreatic secretion.[135, 136] Whether parenteral nutrition stimulates the pancreas in acute pancreatitis is not clear. If there is an effect, clinically that effect remains small and is likely not significant. When compared with the fasted state and intravenous fluids, TPN appears not to exacerbate acute pancreatitis.[124]

TPN clearly is an easy method of providing calories to patients. Several studies have shown that the provision of TPN does maintain nutritional status. Albumin, transferrin and nitrogen balances were improved after the administration of TPN.[124, 137, 138] However, despite providing successful nutrition, the outcome from pancreatitis remains unchanged. Early studies using TPN suggested a reduction in mortality rates associated with TPN.[125] However, these findings were not reproduced in subsequent case series data[137, 139] or in the only randomized study comparing TPN to the fasted state in pancreatitis.[124]

The use of parenteral nutrition has been associated with an increased risk of infection and septic complications when compared with patients receiving TEN in a variety of diseases. There are two reasons for this. First, with central venous catheters there is the possibility of catheter-related sepsis or blood stream microbial invasion. Reported rates of catheter related sepsis range from 9 to 17% in patients with pancreatitis which is significantly higher than other diseases. Second, concerns have been raised about bacterial translocation of the gastrointestinal tract in patients receiving TPN causing distant sites to become infected with gut bacterial flora. Enteral nutrition theoretically uses the gut and minimizes translocation thus reducing infection. No study has made a clear association between catheter-related sepsis or translocation and secondary pancreatic infection.

Total Enteral Nutrition

About the same time TPN was gaining acceptance in supporting acute pancreatitis, it was shown that an elemental diet infused into the jejunum of patients with complicated pancreatitis could be well tolerated.[140] Enteral nutrition remained in the background because TPN was easily administered, bypassed the gastrointestinal tract and appeared to minimize pancreatic stimulation. However, the concept of enteral nutrition in supporting acute pancreatitis has enjoyed a revival in the literature largely because of the high rates of catheter-related sepsis and a lack of effect of TPN on modifying the outcome of pancreatitis. Moreover, studies from the trauma and burn management have show enteral nutrition to have fewer complications, be a potential for immune modulation and disease attenuation, a reduced incidence of sepsis[65] and less expense.

To be able to use enteral nutrition and maintain pancreatic rest requires a basic knowledge of pancreatic exocrine physiology. Pancreatic exocrine stimulation occurs in three phases: cephalic, gastric and intestinal. The cephalic phase is a response to the sight, smell and taste of food. G cells release gastrin in response to vagal cholinergic, adrenergic and dopaminergic mechanisms. In turn, gastrin stimulated HCl release by oxynitic cells in the stomach. The gastric phase relies on gastrin to directly stimulate pancreatic output by directly inducing protein release from acinar cells and indirectly by lowering the pH within the duodenum to produce secretin. Secretin stimulated the pancreas to produce the bicarbonate-rich pancreatic secretions. Chyme passage into the duodenum also stimulates pancreatic secretion through gastric distension. The intestinal phase is signaled by the entry of chyme into the duodenum. Cholecystokinin-pancreozymin (CCK) is released in response to amino acids, oligopeptides, long-chain fatty acids and monoglycerides found at the bowel mucosa. CCK remains a potent stimulator of pancreatic protein secretion and is released in decreasing amounts from duodenum to jejunum. Therefore, jejunal feeding should minimally stimulate the pancreas.

Several canine studies infused elemental diets into various parts of the gastrointestinal tract. Oral, gastric and duodenal infusions clearly showed an increase in pancreatic secretions, but as the infusion is moved more distally, the volume of pancreatic secretion is reduced.[132] Jejunal administration of enteral nutrition in canines produced a secretin-like response from the pancreas but lacked pancreatic protein secretion.[141] This study concluded that jejunal feeding did not rest the pancreas because it did induce a

secretory response, but that there was a failure to stimulate enzyme production, which would propagate the pancreatitis. Human studies using patients with chronic pancreatitis showed only a minimal change in pancreatic secretion.[142, 143] Like parenteral nutrition, there is no conclusive evidence that enteral nutrition does or does not stimulate the pancreas.

In humans, enterally-based nutritional supplements range from blenderized meals or hydrolysate to elemental formulations that provide protein, fat and carbohydrate components on a molecular level. Excluding hydrolysates, there are two categories of enteral nutrition: polymeric and elemental. Polymeric formulations generate 30% of their calories from long chain triglycerides or fat. Comparatively, elemental formulations only generate 10% of their calories from fat in the form of medium chain triglycerides, which do not require pancreatic digestion or micellar solubilization for absorption. Additionally, there are even more specialized elemental feeds that are touted to be immune modulating, inflammation attenuating or intestinal stabilizing because of added nutrients such as glutamine. Selection of an enteral product needs to be based on several factors including gut function, site of delivery (stomach vs. intestine) and disease state.

Enteral feeding has been shown to be possible and safe in several human studies.[140] [7, 144] [145] Further evidence of the success of enteral nutrition has been gathered through several controlled trials. (Table 4-1)

McClave et al[8] randomized 30 patients over 32 admission with an average Ranson's score of 1.5 and APACHE III score of 17 to receive either TPN or TEN. Patients were provided 25 kcal/kg/day and 1.2 g/kg/d of protein starting 48 hours after admission. The study concluded that TEN is safe, effective and less costly than TPN. They also concluded that TEN might promote more rapid resolution of the stress response to pancreatitis. One of the difficulties with this study is that mild and severe pancreatitis was included together. Most mild pancreatitis does not require nutritional support and even many severe pancreatitis (by Ranson's criteria) will not require nutritional support if allowed to settle for several days. In addition, while costs were analyzed and showed that TPN was more costly, there was no formal economic evaluation.

Similarly, Kalfarentzos et al[9] enrolled 38 patients with an average Imrie score of 4.2 - 4.6 and APACHE II score of 12.7 to receive TPN or TEN. Patients were provided 30 – 35 kcal/kg/d and1.2 – 1.5 g/kg/day of protein. This study showed both types of nutrition could deliver a minimum caloric level with similar trends toward a positive nitrogen balance. Patients receiving TPN had more hyperglycemia and more sepsis related events.

Additional emphasis has been placed on the gut during acute pancreatitis as a source of cytokines driving the systemic inflammatory response. Using the gut with enteral nutrition has theoretically been touted as being able to reduce the inflammatory response. Windsor et al[10] randomized 34 patients with an average Glasgow score of 2 and APACHE II score of 9.5 to receive TEN or TPN. Each patient received a standard

nutritional formula for a period of seven days. The inflammatory response by C-reactive protein, Endo Cab Antibodies and total antioxidant capacity was followed and it was concluded that TEN did attenuate the inflammatory response.

Powell et al[146] randomized 27 patients with a median Glasgow score of 4 (range 1 – 6) and APACHE II score of 10 – 12 to receive TEN or conventional therapy of intravenous fluids and nil per mouth. Enteral nutrition was provided at a variety of rates and the inflammatory markers C-reactive protein and IL-6 were followed. No difference between TEN and NPO was found in moderating the inflammatory response within the first 4 days. Patients with mild pancreatitis were included in this study and likely did not require nutritional support and may have altered the change in inflammatory markers. Despite the mild pancreatitis, patients were only able to tolerate a median 21% of their nutritional requirements and progressed to diet as tolerated within 4 days. A secondary finding in this study was that intestinal permeability was increased with enteral nutrition as measured by a differential sugar permeability test. This finding is in direct contrast with other research suggesting that intestinal permeability is decreased with enteral nutrition.

The choice of nutritional support for patients with severe pancreatitis remains uncertain. Studies of enteral nutrition have mostly used patients with mild pancreatitis who are unlikely to require or benefit from nutritional support. Nutritional regimens do not appear to be comparable between both groups or to mirror the practice of managing pancreatitis in our center. TPN is clearly easier to administer and delivers a more

consistent level of calories and protein, but it remains unevaluated by economic evaluation methods and is marked by problems of catheter related sepsis and increased levels of sepsis related events.

5.0 METHODS

The ideal choice for nutritional support in severe pancreatitis remains controversial. Accordingly, this is a randomized, controlled trial comparing TPN with TEN for patients with severe pancreatitis. The null hypothesis is, "**TEN is as effective as TPN in reducing the number of days of elevated inflammatory markers including C-reactive protein and Lipase**". A shorter duration of inflammation would clinically translate into earlier oral intake, maintenance of nutrition and thus shorter hospital stays. Our additional research aims are to compare the following in these two modalities of nutritional support: influence on the natural history of pancreatitis, evidence of effective nutrition. cost of effective nutrition, complications of feeding modality, and complications of pancreatitis

Patients with pancreatitis of all etiologies were identified at Edmonton's Royal Alexandra, University and Grey Nun's Hospitals and screened for eligibility. Eligible patients were required to have acute or acute-on-chronic pancreatitis that is the most responsible reason for admission, a Ranson's score of 3 or greater and inablity to tolerate oral intake of clear fluids after a maximum of ninety-six hours of nothing per os since entering hospital. Patients were excluded if they did not meet the above criteria or, if the patient was less than 18 years of age, unable to accept enteral nutrition via the gastrointestinal tract or already receiving nutritional support. Patients with enterocutaneous fistula, "short gut syndrome", Crohn's disease or ulcerative colitis were, thus, excluded.

Patients who met these criteria were offered participation in the study. Informed consent (Approved: University of Alberta Health Ethics Research Board) was obtained by the study investigators or research nurses. Patients were randomized to receive either TPN or TEN in blocks of twenty-five by means of sealed, opaque envelopes.

Therapeutic Intervention

Figure 5-1 outlines the therapeutic intervention. Nutritional support was provided to enrolled patients within a maximum of 5 days from presentation to hospital and without oral intake. The nutritional regimen provided 25 kcal/kg/day and 1.5 g/kg/day of protein. In the TPN group, long-term vascular catheters were placed percutaneously, confirmed radiographically and TPN infused with a 10% dextrose solution at half of the calculated caloric requirements and increased over 2 days to 100% of the target caloric rate. In the TEN group, nasojejunal feeding tubes were placed via endoscopy, confirmed radiographically and Peptamen™, an elemental product with low fat content, infused at 25 mL per hour and increased by 10 mL per hour every 6 hours until the target rate is achieved.

Failure to provide adequate nutrition was defined in the following three instances. First, patients randomized to the TPN group who developed TPN induced cholestasis were considered a TPN failure if the cholestasis did not respond to a reduction in carbohydrates by 25% for two consecutive days and, if necessary, followed by cycled TPN for two days. Patients who did not resolve were converted to TEN.

Second, patients randomized to TEN who were unable maintain placement of the NJ tube were considered TEN failures if they were confused and self removed more than one nasojejeunal tube despite medical treatment of confusion, and physical and chemical restraints. Failures were converted to TPN.

Third, patients randomized to TEN who after 5 days of enteral feeding were not receiving 50% of maintenance calories were considered TEN failures and were supplemented with peripheral parenteral nutrition or TPN until maintenance calories could be provided.

The attending physician and the house staff independent of the study instituted a gradual oral diet starting from clear fluids and progressing to full fluids and diet as tolerated. Calorie counts were instituted when patients were placed on a full fluid diet. When patients were able to tolerate 50% of their maintenance caloric requirements on a full fluid diet, the rate of TPN or TEN was halved. When the patient achieved this goal and started on diet as tolerated the TPN or TEN was stopped. Patients who tolerated diet as tolerated and were able to maintain their caloric intake for 24 hours were discharged from the study.

Measures of Nutrition and Inflammation

Indices of nutritional adequacy were collected twice per week. These included complete blood count, electrolytes, AST, ALT, lipase, bilirubin, alkaline phosphatase, serum albumin, pre-albumin and blood sugar monitoring. In addition, a 24-hour urinary nitrogen balance was obtained each week and after 24 hours of a full fluid diet.

Indices of inflammation were also collected twice per week. These included lipase and C-reactive protein levels. Serum CCK was obtained to assess the level of pancreatic stimulation to the institution of nutrition. CCK levels were drawn just before to initiation of nutritional support and after 24 hours of nutritional support.

Patients at the Royal Alexandra Hospital and University of Alberta Hospital sites underwent indirect calorimetry via Metabolic Cart on the day of enrollment and after five days of nutritional support provided they were not on supplemental oxygen or in renal failure. Intubated patients were eligible for indirect calorimetry through a closed loop ventilatory system. Indirect calorimetry was not available at the Grey Nun's site.

Physicians who manage pancreatitis make decisions regarding nutrition, in part, by the patient's description of the amount of pain and by the amount of narcotic. Patients whose pain is settling and who have decreasing narcotic requirements generally had their diet advanced. A modification to the study protocol was made six months into the trial to follow patients pain levels. Patients were asked to rate the degree of pain they had been experiencing over the preceding 24-hour period using a visual analog scale. In addition, the amount of narcotic equivalents were charted for the same period of time. To correlate this with key measures of inflammation, the pain score and narcotic counts were obtained at the same time the serum measures of nutrition were collected. Intubated patients were ineligible to rate the degree of pain with the visual analog scale because of the presence of sedative medications to maintain intubation.

Measures of Cost

Indices of cost were collected for every patient enrolled in the study. Measures of cost were captured through several means. First, the direct marginal cost of nutrition was determined by calculating the cost per milliliter of nutrition for each nutritional group and capturing the volume of nutrition for each patient. Indirect costs for overhead were allocated to the cost of producing TPN, to the cost of endoscopic placement of the nasojejunal tubes and to the insertion of PICC lines for TPN. Second, direct radiological costs per patient were captured for computed tomography, ultrasound and insertion of percutaneous drainage catheters after defining a unit cost for each investigation. Third, the cost of serious adverse events or morbidity were determine using two methods: for patients undergoing an operative procedure, direct patient costs including overhead were obtained from the Regional Costing Office of the Capital Health Authority and for non-operative complications an average per diem cost for general care and intensive care was calculated and applied to the length of stay associated with each complication.

A formal economic evaluation using a cost-effectiveness methodology was conducted in parallel to the clinical study. Cost effectiveness ratios were calculated using the formula described in Drummond et al.[20] The ratio is determined by dividing the differences in cost by the differences in outcome:

$$CER = \frac{\text{(Cost of strategy two – Cost of strategy one)}}{\text{(Unit of outcome two – Unit of outcome one)}}$$

For this analysis, a regional health authority or hospital-based perspective was used as a basis to determine which costs were included. The costs were not discounted considering

the short duration of the study period. Similarly, the effects or outcomes were not discounted.

To analyze and account for cost variability, a one-way sensitivity analysis was completed. Three different scenarios were examined and the cost effectiveness ratios re-calculated. First, it was assumed each patient would use only one nasojejunal tube. Second, it was assumed that there were no TEN failures. Third, it was assumed that there were differences based upon the duration of nutrition and an arbitrary threshold of ten days was chosen. If the treatment groups were found to be equivalent in terms of nutritional effectiveness, the intent was to change the cost-effectiveness analysis to a cost-minimization strategy.

Outcomes

Primary outcomes for clinical effectiveness of nutritional support include natural history of pancreatitis (eg. days to normalization of inflammatory markers, days to first oral feeding, duration of elevated lipase); indices of adequate nutrition (eg. 24-hour urinary urea, albumin, metabolic cart analysis); catheter or feeding tube complications (eg. infection, erosion, bleeding, thrombosis); incidence of complications of pancreatitis (eg. pseudocyts, necrosis, infected necrosis)

Secondary outcomes included data to define the cost of each type of nutrition and the associated radiology, interventional and length of stay costs. As part of this, the incremental cost-effectiveness ratio per reduction in days of elevated inflammatory markers was to be determined.

Statistical Analysis

To observe a difference between the groups, the total sample size was estimated at 58 participants to achieve an alpha = 0.05 and a beta = 0.2). Based on a review of the literature, we conservatively assumed a clinically important difference to be a mean of 2 days to achieve a 50% reduction in C-reactive protein levels with a standard deviation of 3 days. Data were collected using a standardized computer database (Microsoft Access 2000) and transferred into the Statistical Package for the Social Sciences (SPSS 10) for analysis. Statistical analyses were performed on an intention-to-treat basis. They consist of descriptive and comparative statistics including parametric (t-tests, chi-squared) and non-parametric (Mann Whitney U) tests.

6.0 RESULTS

From July 15, 1999 to December 31, 2000, 548 cases of acute pancreatitis were screened for potential enrolment into this study. (Figure 6-1) Of those, 135 patients had a Ranson's severity score of three or greater. 110 patients were excluded because they tolerated oral intake within 5 days of admission (89), died during the screening period (5), were enrolled in other studies (2) or met other exclusion criteria (3). 36 patients met all inclusion and exclusion criteria and were eligible for consent. Six patients refused to participate and the study team did not identify five patients. In all, twenty-five patients consented to participation and completed the study. 15 were randomized to total parenteral nutrition and 10 to total enteral nutrition.

Table 6-1 shows the demographic distribution and baseline characteristics of the two groups. They are similar in terms of gender distribution and age. Gallstones were the most common etiology in both groups followed by alcohol and idiopathic. The average Ranson's score was greater than 4 and no patient had a score less than three. APACHE scores showed a similar level of severity with average admission scores of 12. CT grade, as assessed by Balthazar et al[97], was grade C (A = 1, E = 5) or worse. When compared to those patients, who refused to participate, were not identified or enrolled in other studies, the study population was similar in gender, age, severity of disease and underlying co-morbid disease, but there was a trend toward more hypertension and heart disease. (Table 6-2)

Reduction in Inflammation

The reduction in inflammation in terms of C-reactive protein between the two groups was on average of 2.6 days faster for TEN than TPN (p = 0.171; 95% CI of the time difference = -1.2,6.5). A 50% reduction in C-reactive protein was achieved in the TEN group at 7.6 days compared with the TPN group that required 10.2 days to achieve the same reduction. (Table 6-3) Changes in serum lipase levels showed the opposite result. A 50% reduction in lipase was achieved in the TEN group at 6.7 days compared to the TPN group that required 4.3 days to achieve the same level of reduction. (p = 0.608; 95% CI of the time difference = -12.2,7.5)

Measures of Effective Nutrition

At enrolment into the study, the baseline nutritional status was similar for both groups in terms of percent ideal body weight, albumin, pre-albumin and 24-hour urinary nitrogen levels. (Table 6-4) Patients were also held fasting for a similar number of days before the initiation of nutritional support.

The ability to deliver and provide nutrition was not different between the two groups. (Table 6-5) Patients randomized to TPN achieved the 25-kcal per kilogram target level in an average of 2.1 days compared with 3.3 days for patients receiving TEN. (p = 0.259; 95% CI of the time difference = -3.4, 0.97) While enrolled in the study, patients receiving TPN were provided an average of 21 kilocalories per kilogram per day compared with 18 kilocalories per kilogram per day while on TEN. (p = 0.164; 95% CI of the caloric difference = -1.2, 6.8) However, patients receiving TEN had this as their sole

source of nutrition for 13 days and took 12 days to tolerate a full fluid diet and 15 days to tolerate diet as tolerated. Similarly, TPN patients had this as their sole source of nutrition for 12 days and took 12 days to tolerate a full fluid diet and 13 days to tolerate diet as tolerated.

After nutrition was instituted, each patient's nutritional status was monitored by pre-albumin levels twice-weekly and 24-hour urinary nitrogen balances weekly. Both groups appeared to achieve a neutral metabolic state with equivalent nitrogen balances (Figure 6-2) and increasing pre-albumin levels at the time of discharge from the study. (Figure 6-3) In addition, nutritional status was measured in selected patients able to undergo indirect calorimetry via metabolic cart testing. Patients receiving TPN had higher than predicted resting energy expenditure levels by indirect calorimetry; whereas, TEN patients were reliably estimated by using the 25 kilocalories per kilogram per day estimation of resting energy expenditure. (Figure 6-4) The respiratory quotients prior to initiation of nutritional support and after 7 days of nutritional support were similar in both groups at 0.70. (Figure 6-5)

The test of pancreatic stimulation, serum CCK, showed pre and post nutrition levels to be similar before and after removal of a single outlier in the TEN group. A standard scatter plot and probability plot revealed this value to be significantly different than the others. This in combination with laboratory concerns about the accuracy of this test result led to its removal from the analysis. Patients receiving TPN had pre-nutrition levels of 27 pmol/L and after 24 hours of nutrition of 21.6 pmol/L. Similarly, patients receiving TEN

had pre nutrition levels of 56.8 pmol/L and post nutrition levels of 55.7 pmol/L. (Figure 6-6)

Pain Assessment

The patient's perception of pain was evaluated by means of a visual analog scale and capture of the narcotic requirements as measured in milligrams of morphine equivalents. These were measured to correlate with the key measures of nutrition and inflammation. Only 3 patients were able to reliably complete the visual analog scale. Patients admitted to the intensive care unit were usually sedated to maintain intubation and thus were not candidates for completion of a pain score. In general, these three patients showed a decreasing amount of pain during the study and had no pain at the time of discharge from the study.

Narcotic usage was difficult to track despite a computerized drug system at one site. Data was gathered for 7 patients (3 TEN; 4 TPN). TEN patients used an average of 25 mg of morphine equivalents at the beginning of their illness and no narcotics on discharge. TPN patients used an average of 29 mg of morphine equivalents at the beginning of their illness and 28.5 mg of morphine equivalents at discharge from the study. The values between the groups were not statistically different.

Mortality

During the study period 8 deaths were identified with a Ranson's score > 2 for a mortality rate of 5.9% (8/135) in all patients screened with a Ranson's score > 2. Five deaths

occurred within the screening period and were not included in the study. There were three male patients (8.3%) who died while enrolled in the study. All three patients were randomized to the TPN arm of the study. All three deaths were externally reviewed and were attributed to specific complications of pancreatitis and not to the nutritional modality. Table 6-6 outlines the characteristics of these patients. Patient A died shortly after starting nutritional support. Patient B died after 4 days of nutritional support. And, patient C was supported through to the end of the study period of 30 days only to succumb to septic complications of the disease almost 4 months later.

Morbidity – Secondary to Pancreatitis

Morbidity or serious adverse events due to complications of pancreatitis were tracked for both arms of the study (Table 6-7). In addition to the three deaths, eight patients developed acute pancreatic fluid collections or were forming pancreatic pseudocysts that were identified on CT scanning. Three patients, in the TPN group, developed infected pancreatic fluid collections and required operative debridement. One patient grew an isolated culture of Staphylococcus epidermis. Another patient returned approximately 14 days after discharge with a history, exam and radiologic investigations consistent with an infected pancreatic fluid collection. A third patient continued to worsen clinically in the intensive care unit and required laparotomy and drainage of an infected pancreatic collection. Intra-operative cultures in the latter two patients were polymicrobial.

One patient, in the TEN group, underwent ultrasound-guided percutaneous aspiration of a pancreatic fluid collection for a intermittent and persistent fever and equivocal radiologic

findings. After drainage, the patient continued to have a fever and failed to progress off TEN. The patient subsequently was found to have two small enterotomies secondary to the percutaneous drainage catheter at laparotomy. Intra-operative cultures were polymicrobial.

Additional complications of pancreatitis included the development of acute renal, respiratory, cardiac and hepatic failure. Three patients developed post-pancreatitis diabetes that required insulin treatment.

Morbidity – Secondary to Nutritional Practices

Morbidity or serious adverse events due to either method of nutritional was also tracked (Figure 6-8). There were no major complications related to the insertion of PICC lines or placement of nasojejunal tubes for nutritional support. One patient with a PICC line developed a hematoma, which was managed with pressure and compresses. In the TPN arm, one patient was identified to have developed an infected pancreatic fluid collection with Staphylcoccus epidermis. The origin of the bacteria was likely from the PICC line. Unfortunately, the laboratory lost the confirmatory PICC tip culture.

In the TEN arm, 90% of patients with NJ tubes either pulled out or dislodged the nasojejunal tube; thereby, requiring temporary or early cessation of TEN. 50% of patients suffered diarrhea in this group requiring control with thickening agents or medication. One patient in the TEN arm developed a gram-negative bacteremia prior to enrolment in the study. There was one TEN failure in the study. This patient developed

delirium tremens and in his delirious state self removed his nasojejunal tube. It was felt that he would continue to remove nasojejunal tubes and he was therefore converted to TPN.

Nearly 75% of all participants were found to have a blood glucose level greater than 11.0 mmol/L/day during the delivery of nutrition. 80% of patients receiving TPN had an average of 3.6 days of elevated blood glucose levels compared to 60% of patients on TEN who had an average of 2.7 days of elevated blood sugars.

Cost of Nutrition

The individual components of the cost inventory for the study are contained in Appendix A. The average cost of TPN was $1,968.62 compared to the average cost of TEN at $1,207.83 (p = 0.236; 95% CI of the cost difference = -416.12, 1601.81). The cost of radiologic investigations was $732.75 for the TEN arm and $792.36 for the TPN arm (p = 0.756; 95% CI of the cost difference = -332.67, 451.89). The overall cost for the entire length of stay was $15,586.60 in the TEN arm and $14,680.13 in the TPN group (p = 0.896; 95% CI of the difference = -15,154.00, 13,341.07).

The cost of serious adverse events was calculated if the care of the complication was deemed to increase the length of stay or was in addition to the usual care being provided to patients with acute pancreatitis. Therefore, acute pancreatic fluid collections, diabetes, PICC line hematomas, diarrhea, gram negative bacteremia and elevated blood glucose were not assigned a cost. Acute organ system failures were grouped together and a cost

assigned based upon the number of days spent in the intensive care unit (ICU). Patients assigned to TEN had an average ICU cost of $21,022.11 and those assigned to TPN a cost of $11,750.60. There were an additional 5 nasojejunal tubes placed costing a total of $2,888.25

Infected pancreatic fluid collections generated the most additional cost. These costs include the cost of operative drainage, operating and recovery room costs, and direct nursing care for the post-operative period. The cost for the patient assigned TEN was $10,740.52 and the average cost for the three patients assigned to TPN was $12,768.65.

A one-way sensitivity analysis was performed. Four scenarios were analyzed. First, patients were assumed to require one nasojejunal tube placement. The rate of dislodgment or removal was greater than 90%. Previous studies have suggested that one nasojejunal tube is sufficient. Alternative methods for placement of these tubes can be used to achieve this target. Second, one patient who was a TEN failure only received three hours of nutrition. With better patient selection for nasojejunal tubes, this patient would not have received a feeding tube in alcohol withdrawal. Therefore, this patient was assumed to have received TPN only and all other nasojejunal patients provided with one tube. Third, patients receiving greater than ten days of nutrition were analyzed. And, fourth, those receiving less than ten days of nutrition were assessed.

Table 6-9 shows the results of the sensitivity analysis. In the first scenario, the average cost of TPN is $1,968.62 compared with $1,086.89 for TEN ($p = 0.72$; 95% CI of the cost difference = -86.17, 1,849.63). When scenario two is incorporated with the first

scenario, the difference in cost widens to $956.40 (p = 0.042; 95% CI of the cost difference = 13.44, 2,010.40). In the third scenario, patients requiring nutritional support for greater than ten days have an average cost of $2,800.47 for TPN and $1,580.92 for TEN (p = 0.072; 95% CI of the cost difference = -381.98, 2,261.45). For patients requiring less than ten days of nutrition, the difference in average cost was $325.75 (p = 0.365; 95% CI = -457.14, 1108.64).

Cost-Effectiveness Analysis

Cost-effectiveness ratios are usually calculated using the formula on Page 51. However, in this study, the primary result shows that the cost of TEN is less than the cost of TPN in all situations (see sensitivity analysis) and that the reduction in inflammatory markers showed a trend to greater reduction with TEN. These results produce a situation where TEN is both less costly and produces an equivalent outcome: reducing inflammation. In these circumstances there is no need to calculate a cost-effectiveness ratio because the interpretation is clear: adopt technologies which cost less and produce equivalent or better effect.[147] Thus, TEN becomes a dominant technology over TPN with respect to cost-effectiveness.

7.0 DISCUSSION

Previous studies of patients with acute pancreatitis have proven the ability to deliver enteral nutrition,[7, 8, 140, 144] have shown enteral nutrition is associated with less complications[9] and have demonstrated a moderation of the acute phase response with enteral nutrition[10]. No study has compared parenteral to enteral nutrition in severe pancreatitis in terms of reducing inflammation with a parallel cost-effectiveness analysis. The present study has confirmed that enteral nutrition can be delivered safely in severe pancreatitis, has similar complication rates to parenteral nutrition and supports a trend toward faster moderation of the acute inflammatory response. It has further shown that enteral nutrition is a dominant technology in terms of cost effectiveness compared with parenteral nutrition.

Unfortunately, this study is limited by its small sample size. The incidence of severe pancreatitis, as defined by a Ranson's score greater than or equal to three, in this study (25%) is consistent with other reported rates of severe pancreatitis. However, in an attempt to enroll a truly severe group of patients with pancreatitis, tolerance of clear fluids within 5 days of admission was added and reduced the eligible population for this study. The corollary is that this study has truly enrolled patients with severe pancreatitis who require nutritional support. The rates of refusal and patients not identified by the study team were somewhat high and this was also found in other studies.[8] Refusals usually were because patients did not want to have a "tube in their nose" even though they were reassured that the nasojejunal tubes were well tolerated by other patients in the study. Patients not identified by the study team were difficult to trace within the hospital

system, but better screening procedures could reduce this number and increase the number of enrolled patients.

Based on the sample size of 25 patients, it appears that TPN is equivalent to TEN in achieving a 50% reduction in inflammatory marker levels – the null hypothesis. The power of this study, with a mean difference 2.6 days, standard deviation of 4 days (effect size 2.6/4 = 0.65) and alpha = 0.05 is approximately 45%. This result is not surprising given that less than half of the estimated sample size has been accrued. A previous study has produced conflicting results but with mild and severe pancreatitis[10] and two studies found, with small sample sizes, that TEN may not modulate the inflammatory response in pancreatitis.[8, 146]

The power of this study could be enhanced with an achievement of a larger sample size, which in turn results in a narrower standard deviation. If the effect size and standard deviation remain unchanged for the duration of the study, the power of the study would be achieved at a sample size of 30 patients per arm as was originally calculated.

There is a reasonable chance of beta-error in this study because the sample size has not been met and the power of the study is small. However, trends have begun to emerge in terms of attenuation of the inflammatory response and cost-effectiveness of nutrition that suggest there is a difference between the types of nutrition. Additionally, the septic complications found in this study also point to a difference in nutritional types. This

underscores the importance of achieving the estimated sample size and completing the clinical and cost effectiveness study.

In this study, there was a trend in the enteral nutrition group showing a 50% reduction in C-reactive protein (CRP) levels at 7.6 days compared with 10.3 days for parenteral supported patients. A recent study showed similar, but statistically significant reductions in CRP levels. However, the study population was composed of both mild and severe pancreatitis and was only nutritionally supported for seven days.[10] The inclusion of mild pancreatitis is likely to influence CRP levels and have smaller changes as these patients frequently improve within 4 – 5 days. The result from the present study is more likely to be representative despite a small sample size because of the more homogenous group of severe pancreatitis.

Lipase levels in this study were observed to have the opposite trend compared with CRP. There are several possible reasons for this observation. First, lipase is usually not recognized as a true marker of inflammation and so may not follow the same trend as CRP. Second, lipase may be liberated from ongoing destruction of pancreatic parenchyma secondary to the disease process. Lastly, in a similar fashion, lipase may be higher in TEN patients as a reflection of low levels of pancreatic stimulation by the enteral nutrition that was not identified by serum CCK.

Despite a trend to early reduction in inflammatory markers with TEN, this did not translate into earlier transition to oral intake and shorter lengths of stay as originally

hypothesized. Both groups achieved and tolerated full fluid diets at approximately 12 days and patients on TPN progressed to diet as tolerated nearly 2 full days ahead of enterally feed patients. This finding may reflect the nutritional tapering protocol that was used and required patients to tolerate 50% of maintenance calories per os on full fluids before reducing that rate of nutritional support. Enterally fed patients were frequently anorexic secondary to a sensation of fullness where enteral nutrition had to be reduced or stopped to allow for full achievement of the 50% of maintenance calories. In two instances, patients on enteral nutrition developed large pseudocysts, which compressed the duodenum and prevented achievement of full fluid diet.

One of the convenient aspects of TPN is that intravenous nutrition is not subjected to variances related to bowel function, patient confusion secondary to alcohol withdrawal and to investigations requiring patients to be NPO. In this study, patients receiving TEN were provided an average of 18 kcal/kg/day compared to 21 kcal/kg/day for patients receiving TPN. Several reasons can be cited for the lower per kilogram calorie count. First, while ileus has been cited as a concern, there were no difficulties in feeding enterally. The protocol for enteral nutrition required an additional day of incremental feeding to reach calorie targets over TPN. Nasojejunal tubes seem to by-pass an apparent gastric ileus, which fits anatomically with pancreatitis. Most patients in the intensive care unit had both nasogastric and nasojejunal tubes placed for a period of time. Second, patients with enteral nutrition also had their feeds held in preparation for radiologic examinations and other examinations as required by hospital policy; thereby contributing to a period of reduced caloric intake. Third, nasojejunal tubes were at times dislodged or

pulled inadvertently by patients. In these instances, feeds were held until placement could be confirmed to be distal to the ligament of Treitz with plain radiograph or replaced the next day by endoscopy.

It was expected that parenteral nutrition would be able to fully provide 25 kcal/kg/day. However, in the first 48 hours a reduced carbohydrate formulation was used to temper blood glucose levels and thus full caloric levels were not achieved. Additionally, for patients with pancreatitis induced by high triglyceride levels, TPN was provided without lipid emulsion until the serum triglyceride levels were controlled.

Even with the difficulties of feeding enterally and with smaller per kilogram calorie levels, the measures of effective nutrition showed favorable results for enteral nutrition. Urinary nitrogen balances became more positive faster than for patients receiving TPN. Pre-albumin levels also approached normal levels faster with enteral nutrition. Whether this is related to attenuation of the inflammatory response or is due to maintenance of the gut mucosa is difficult to determine. Normalization of pre-albumin levels may also represent hepatic reprioritization of pre-albumin synthesis as the pancreatitis resolved.[148] With greater experience and minor changes to feeding techniques, enteral nutrition delivered at appropriate levels might even have a greater impact.

Pancreatic rest has been the key principle in the management of acute pancreatitis. Physicians have expressed concern over using enteral nutrition in severe pancreatitis for fear of stimulating the pancreatitis and worsening the patient. Animal studies have

shown that CCK is a key marker of pancreatic stimulation.[149] Human studies involving patients with chronic pancreatitis showed that oral intake elevated serum CCK levels, but jejunal administration did not raise CCK levels.[150, 151] In the present study, serums CCK levels in both groups remained relatively stable before and after 24 hours of nutritional supplementation. It appears that neither TPN nor jejunal TEN stimulate the pancreas significantly.

There was not enough data to comment on the pain assessment of patients with acute pancreatitis. The reason for instituting these instruments was to correlate the patient's pain, which under normal circumstances is monitored by clinicians informally, with the levels of inflammation (CRP), timing of oral feeding and resolution of disease. The visual analog scale was simple to use in non-intubated patients, but problematic for patients in the intensive care unit on sedatives. Collecting data on the narcotic usage was expected to be simple as most hospitals guard narcotic administration carefully. However, in two of the three sites, charting of narcotic administration was unclear, unreliable and unusable.

The morbidity and mortality of severe pancreatitis remains significant. In the current study, mortality rates approached 6% for patients with a Ranson's score of three or greater and were 8% for those enrolled into the study. All deaths were reviewed and attributed to multi-organ dysfunction. Despite all three deaths being assigned to the TPN group, it remains difficult to ascribe benefit or harm to the mode of nutrition. The complex inflammatory response of pancreatitis is usually well underway before nutrition

is instituted. Whether early enteral nutrition can be used to modulate the inflammatory response is a matter for additional study.

Infections of acute pancreatic fluid collections represented the major complication in this study. There is no proven causative effect between the type of nutrition and the development of infected pancreatic fluid collections in this study. However, several studies including a meta-analysis have shown that enteral nutrition limits the number of septic complications compared to patients receiving TPN.[65, 152, 153] There is additional evidence showing that enteral nutrition reduces bacterial translocation across the gastrointestinal tract in canine and rodent[154, 155] studies. No human study has been able to directly prove an association with nutrition type.[156]

Previous studies have suggested that use of enteral nutrition could reduce septic complications by minimizing bacterial translocation from the gut. In this study, more patients developed infected pancreatic fluid collections on parenteral nutrition. In one instance, intra-operative cultures of the patient grew pure cultures of Staphylcoccus epidermis. The confirmatory central venous access tip cultures were lost unfortunately, but it was assumed that this was a central line complication. In the sole patient on enteral nutrition, who developed an infected collection, it could not be determined whether this was a de novo infection or whether it was secondary to a complication of a percutaneous drain placement that was through small bowel.

Septic complications related to TPN have also been found in patients with persistent hyperglycemia. Patients in the current study experienced very few days of serum glucose levels greater than 11 mmol/L. Enteral fed patients had one fewer day on average. Whether this had an impact on the septic complications above is undetermined. The protocol used in the study called for an aggressive management of elevated blood sugars including the use of sliding scale insulin.

Clearly, the association of pancreatitis and septic related complications is a key issue. At the outset, the primary outcome of this study was a reduction in inflammatory markers as a measure of attenuating the inflammatory response. Septic events may represent an additional or an alternative primary outcome in future research studies involving pancreatitis because these events represent a tangible clinical outcome that can be observed and measured. As opposed to inflammatory markers, which can be measured, but not observed.

Earlier studies identified significant rates of central complications when delivering TPN. In the present study, there were no significant complications secondary to the insertion of a central line. Percutaneous intravenous central catheters (PICC) were used for the majority of TPN patients and were inserted into forearm veins by specialty trained registered nurses or under fluoroscopic guidance by interventional radiologists. Even though there were no significant complications, PICC lines are still susceptible to infection and being the origin of bacterial seeding.

There were no technical difficulties with endoscopic placement of nasojejunal tubes. 50% of patients developed diarrhea with the initiation of enteral nutrition. All patients were easily controlled with thickener or medicinal agents. One potential problem in this study was the rate of dislodged or inadvertent removal of nasojejunal tubes. Frequently, patients with pancreatitis develop confusion from a variety of etiologies and are prone to tube removal. Physical and chemical restraints do not always protect nasojejunal tubes which are easily "tongued out". Several methods of maintain tube placement have been described and have potential benefit in this population, but they do not prevent the patient from using the tongue to dislodge the tube. In retrospect, had one of these methods been used, the average cost of enteral nutrition will certainly have been lower and the average calories per day provided higher. This would have had a positive effect on the outcomes of the study.

No study comparing TEN and TPN in acute pancreatitis undertook a formal cost-effectiveness analysis. Several recent studies performed limited cost analyses on the cost of nutrition.[8-10] In each study, enteral nutrition had lower calculated costs. However, this method fails to consider the cost per effect of treatment. Our cost analysis confirms that enteral nutrition is less expensive than parenteral nutrition. Thereby, creating a situation where TEN, is less expensive and equally effective. Consider this finding against a simplified version of the guidelines (see figure 7-10) for adoption and utilization of technology by Laupacis et al[147]. Under these guidelines, TEN is a grade A technology that warrants adoption, integration and utilization as far as can be determined, given the limited power of this study.

This must also be viewed in two additional contexts. First, the serious adverse events related to TEN were less than that of TPN. The most serious adverse event is an infected pancreatic fluid collection. In this study, there were 3 infected collections associated with TPN and only 1 with TEN. And, the TEN infected collection was complicated by the placement of a percutaneous drain, which may have been avoided all together. Second, the analysis of costs was completed as an effectiveness trial not an efficacy trial using the most conservative assumptions – that is worst case scenario. Should the sensitivity analysis prove to be true, this would give more value to the findings of the cost-effectiveness analysis.

In this randomized controlled trial of TPN and TEN in supporting severe pancreatitis, primary data have been generated to help support a health technology assessment of two methods of nutritional support – TPN and TEN. This study has confirmed that TEN can be safely delivered to patients with severe pancreatitis without significant complication. Trends have emerged suggesting that TEN attenuates the inflammatory process of pancreatitis, does not stimulate the pancreas and can provide sufficient nutritional support despite provided only 18 kcal/kg. The cost analysis has demonstrated that TEN is less expensive; thereby, creating a situation where TEN is the dominant choice of nutritional support in severe pancreatitis. Adoption, integration and utilization of this technology should proceed, but with knowledge of the limitations of the study. Further research into the association of TEN with septic events in pancreatitis is required.

8.0 CONCLUSIONS AND RECOMMENDATIONS

In this thesis, a health technology assessment approach using primary and secondary data was used to help understand the role of nutritional support in the management of severe pancreatitis. From these studies, it is clear that either TPN or TEN can be used to support acute pancreatitis safely and adequately. The interaction between enteral nutrition and the inflammatory response remains unclear, but trend suggests that TEN does have a role in modulating this response. The present study, through a cost-effectiveness analysis, has asserted that TEN is the dominant nutritional technology over TPN in terms of cost effectiveness and that this technology should be adopted, integrated and utilized in clinical practice.

However, these findings must be viewed with cautious optimism. The small sample size makes it difficult to fully embrace the assertions of the cost-effectiveness analysis. Despite a promising start, further research is required. Three possible strategies exist. First, attempt to achieve the estimated sample size, so that the study achieves its power. Second, move toward a formal meta-analysis or systematic review of the 5 controlled studies without those patients with mild pancreatitis because patient recruitment has been difficult. And, third, combine the first two strategies.

Several areas for additional research have also been identified in the primary study. First, research into the interaction between TEN and septic events in pancreatitis could add additional support for the use of TEN. Second, another confirmatory cost-effectiveness analysis is required to support the assertion of adoption and utilization. And, third, to

increase the application of HTA style research in other areas of surgery will help to define other Grade A - technologies.

The last and most important function of the HTA process is to disseminate and evaluate the findings of the study. Currently, TEN is not the nutrition method of choice for many physicians who manage pancreatitis. Dissemination of this HTA and evaluation of its response will be critical to changing current practices, dispelling currently accepted dogma around pancreatic stimulation and implementing cost-effective medical therapies. A mixture of dissemination methods must be used including conference presentations and publications. However, the key factor in changing the existing practice patterns will be those physicians who have had experience in providing enteral nutrition to patients with severe pancreatitis. The message should focus on the minimal level of pancreatic stimulation and the ability to deliver adequate nutrition to the jejunum.

Ongoing evaluation and feedback to physicians is also required. At the clinical level, nutritional experts and dieticians must provide clinicians caring for pancreatitis with information about the success of providing calories and nutrition. The use of care maps, which would stimulate physicians to use enteral nutrition, is one method of ensuring greater adoption of this technology. Tracking of septic complications should also be undertaken through quality improvement programs to add further evidence for the use of enteral nutrition. At the hospital and regional health authority level, cost-effectiveness information must also be integrated and fed back to physicians.

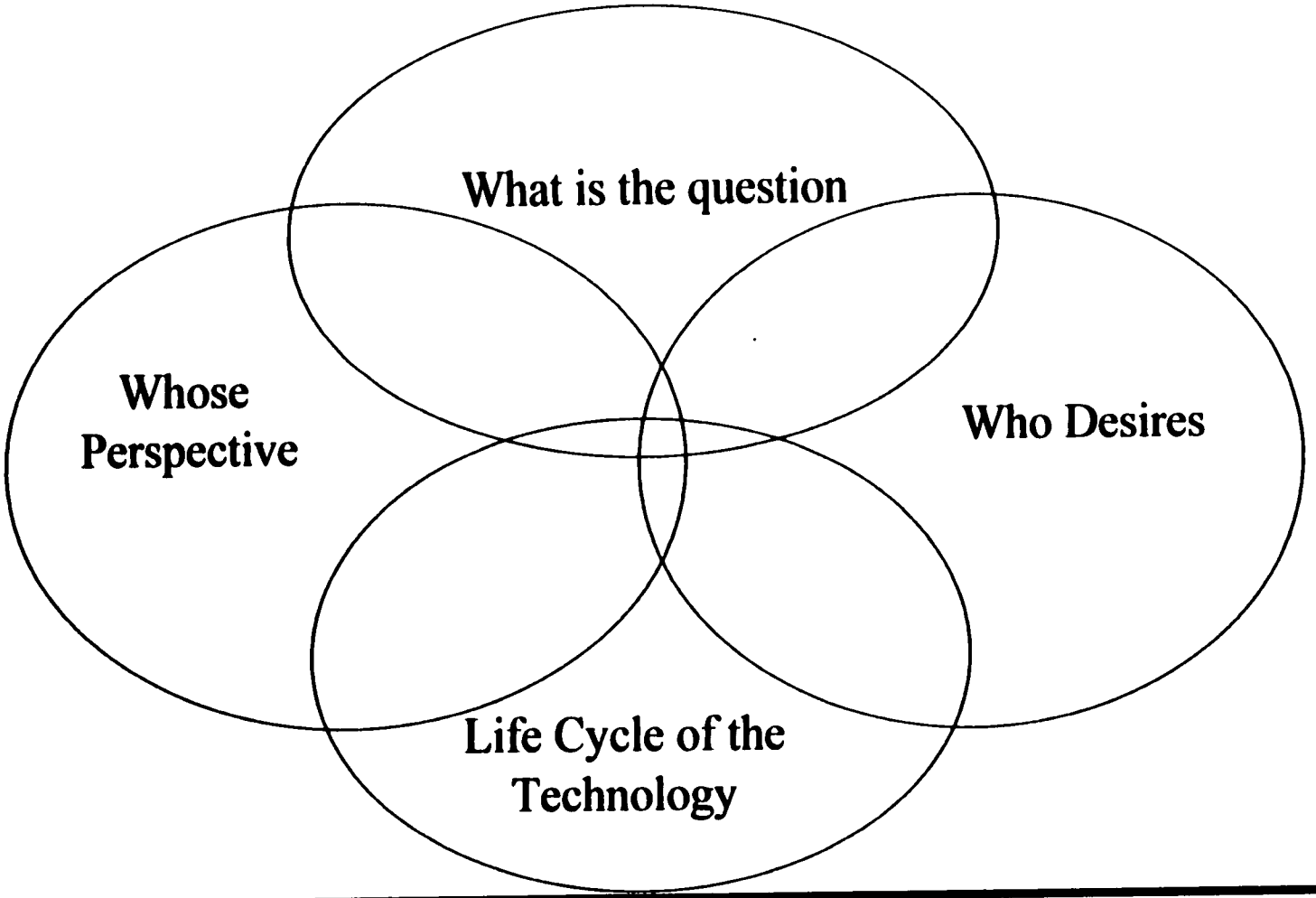

Figure 2-1: Key Factors in Health Technology Assessment

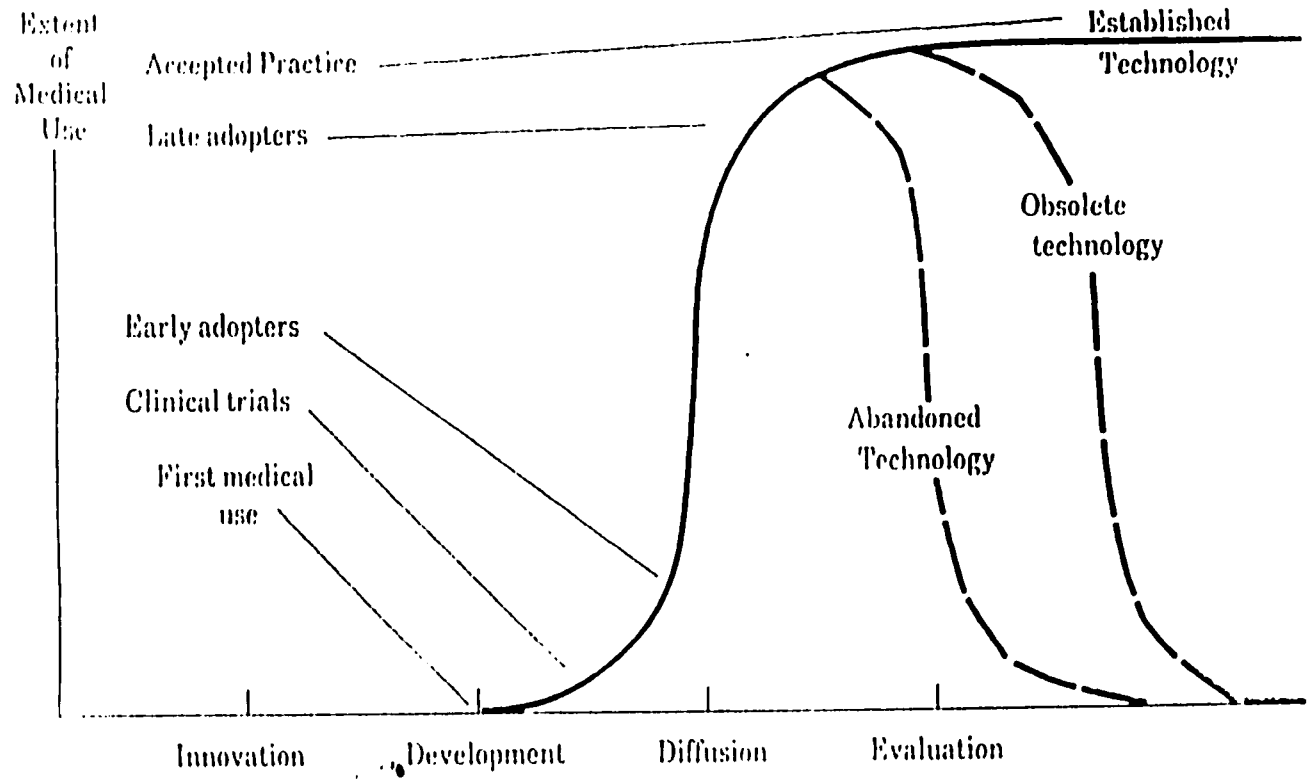

Figure 2-2: Life Cycle of Technology
From: Feeny, D et al. Health Care Technology: Effectiveness, Efficiency and Public Policy. 1986.

Steps in Health Technology Assessment

- Identify and prioritize questions/issues
- Determine perspective and who will perform
- Collect primary and secondary data
- Analyze and interpret data
- Formulate findings and recommendations
- Disseminate findings and recommendations
- Evaluate the implementation of recommendations

Figure 2-3: Steps in Health Technology Assessment
Adapted from: Goodman et al. VA Hospital Primer on Health Technology Assessment

- Alcohol
- Biliary tract disease
- Hyperlipidemia
- Hypercalcemia
- Familial
- Trauma
- Retrograde pancreatography
- Ischemia
- Idiopathic
- Tumor
- Pancreatic divisum
- Ampullary stenosis
- Ascaris infestation
- Duodenal obstruction
- Viral infection
- Scorpion venom
- Drugs

Figure 3-1: Etiology of Acute Pancreatitis

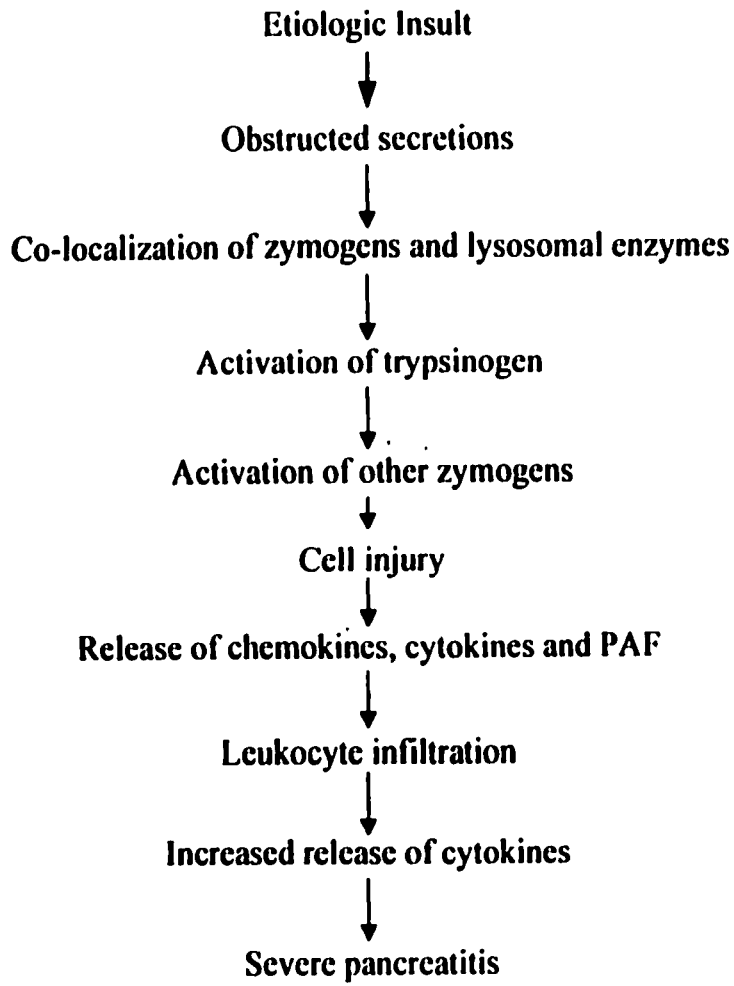

Figure 3-2: Pathophysiology of Acute Pancreatitis
From: Saluja, A and Steer, M. Pathophysiology of pancreatitis. Digestion. 1999;60 (suppl 1):27-33

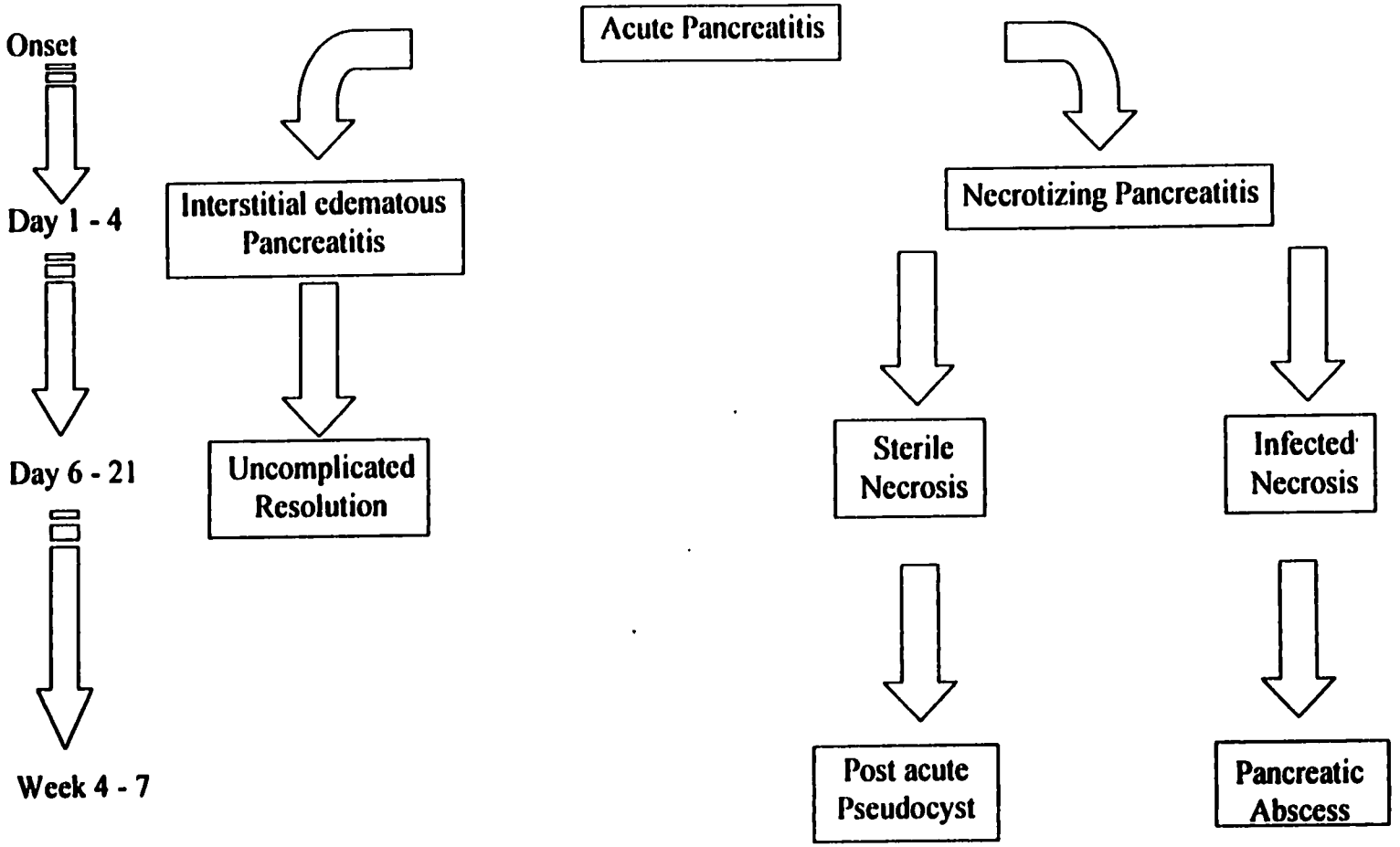

Figure 3-3: Natural History of Pancreatitis
From: Beger, H. et al. Natural Course of Pancreatitis. World Journal of Surgery. 1997; 21:130-135.

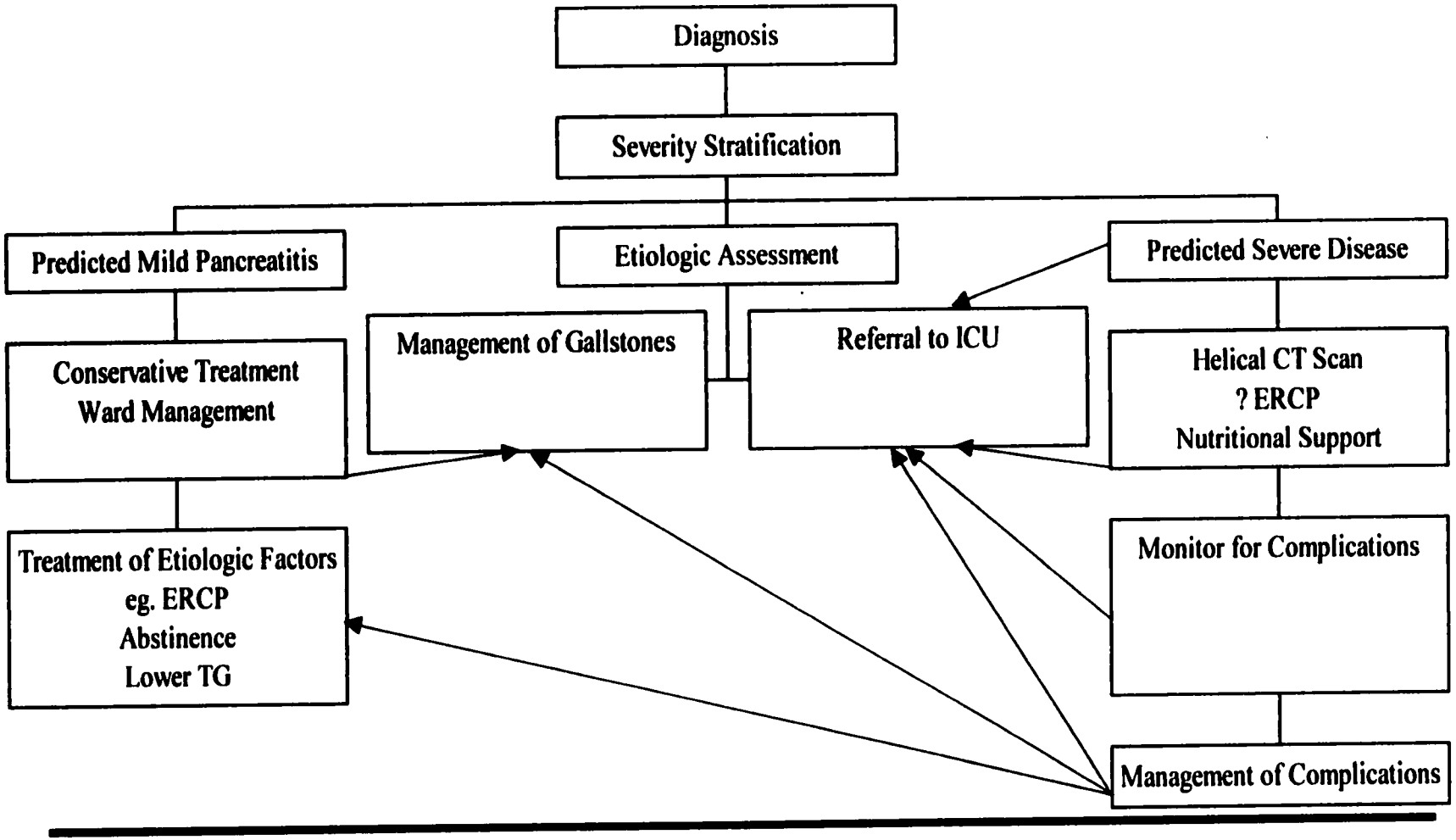

Figure 3-4: Algorithm for the Management of Acute Pancreatitis
Adapted from: United Kingdom guidelines for the management of acute pancreatitis. Gut. 1998;42 (Suppl 2):1-13.

	McClave et al (1997)	*Kalfarentzos et al (1997)*	*Windsor et al (1997)*	*Powell et al (2000)*
Patient Population	16/16 : TPN/TEN Ranson = 1.5 APACHE III = 17	20/18 : TPN/TEN Imrie = 4.2-4.6 APACHE II 12.7	18/16 : TPN/TEN Glasgow = 2 APACHE II = 9.5	14/13 : TPN/TEN Glasgow = 4 (1-6) APACHE II = 10-12
Methods	25 kcal/kg 1.2 g/kg protein Start at 48h	30-35 kcal/kg 1.2 – 1.5 g/kg ptn	7 days Different for mild and severe	TEN vs. NPO Unspecified kcal Start > 72 hours
Outcome	Safe, effective No complications	Safe, effective Min. complicat'ns	TEN better at reducing CRP	Inflammatory response unchanged

Table 4-1: Comparison of randomized controlled trials of enteral nutrition

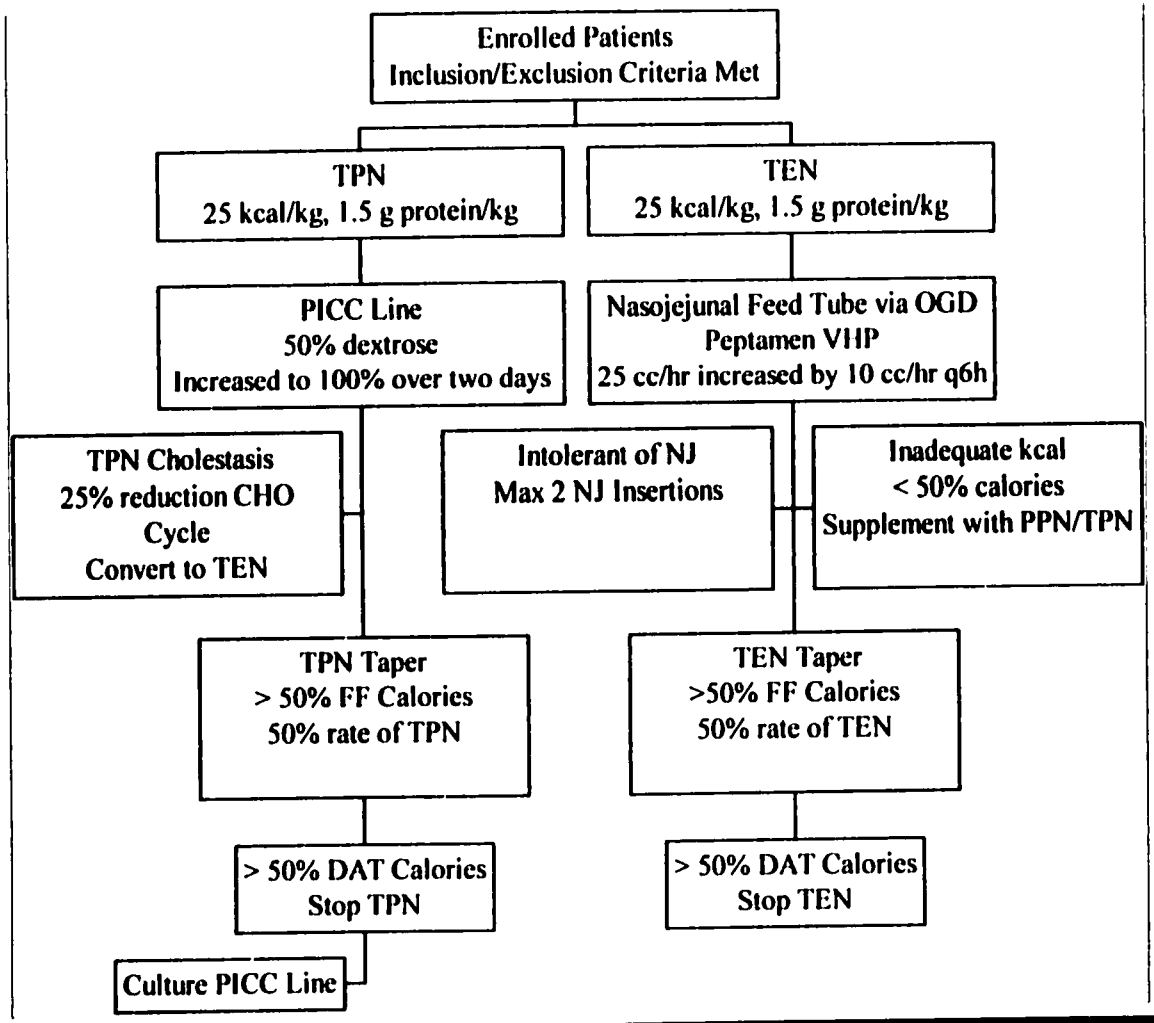

Figure 5-1: Research Protocol

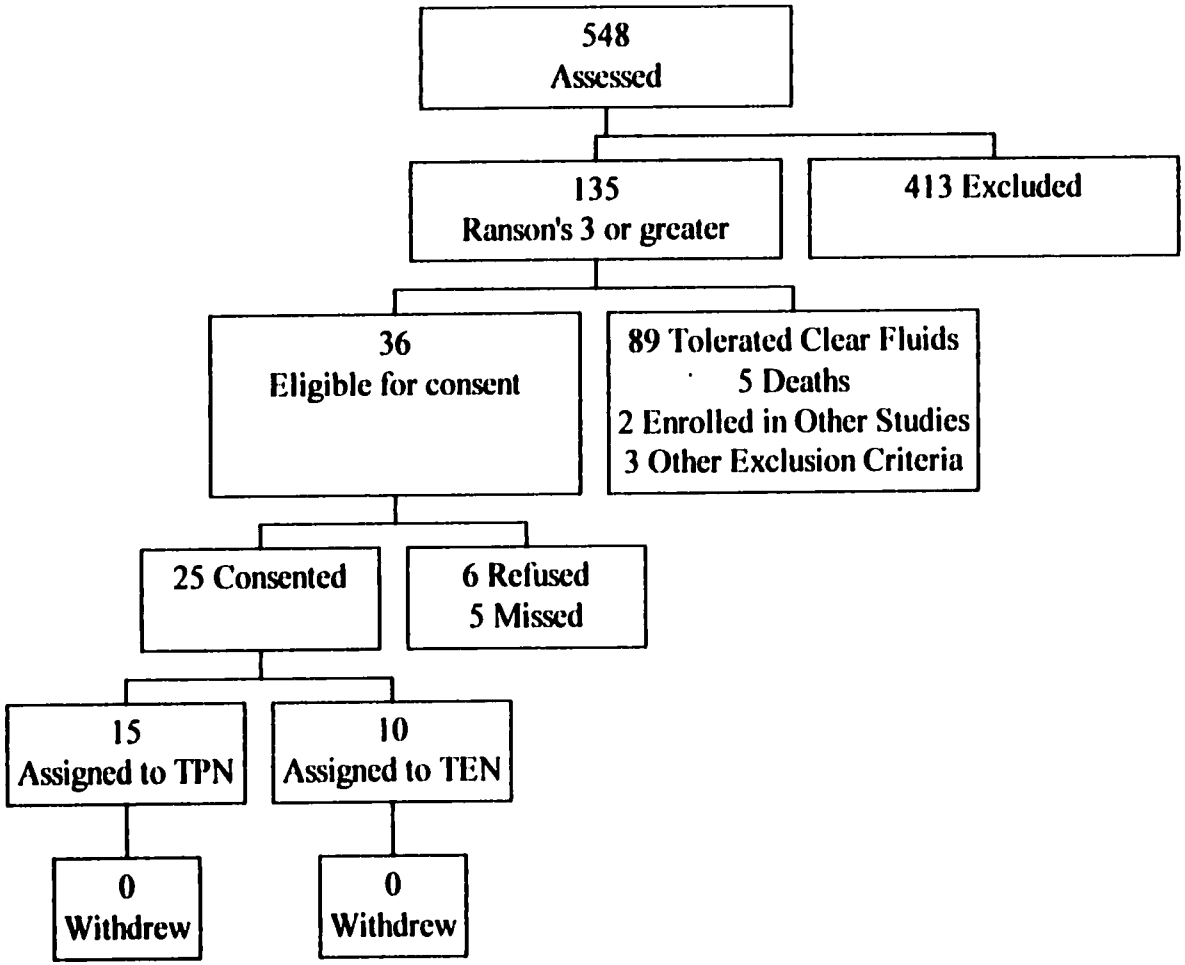

Figure 6-1: Study Enrolment

	TPN	*TEN*
Gender (M/F)	7/8	6/4
Age	61.0 ± 15.6	65.3 ± 18.3
Etiology		
Stones	7	5
Alcohol	3	2
TG	1	1
ERCP	1	0
Idiopathic	4	2
Ranson's	4.5 ± 1.6	4.7 ± 1.3
APACHE	12.0 ± 5.7	11.8 ± 8.3
CT Severity Score	4.0 ± .76	3.4 ± 1.3

(p = not significant)

Table 6-1: Demographics

	Participants	*Eligible Non-participants*
Gender (M/F)	13/12	7/6
Age	62.7 ± 16.5	62.8 ± 18.2
Etiology		
Stones	12	7
Alcohol	5	1
TG	2	2
ERCP	1	1
Idiopathic	6	2
Ranson's	4.6 ± 1.5	4.9 ± 1.5
Co-morbities		
Hypertension	4	9
Heart disease	2	9
COPD	2	2
Diabetes	3	2
Renal Disease	1	2
Cancer	3	1

(p = not significant)

Table 6-2: Comparison of Participants and Eligible, Non-Participants

	TPN	*TEN*	*Mean Difference*	*95% C.I.*
CRP	10.3	7.6	2.6	(-1.2,6.5)
Lipase	4.3	6.7	-2.3	(-12.1,7.5)

Table 6.3: Number of days to a 50% reduction in inflammatory marker levels

	TPN	*TEN*
Percent Ideal Body Weight	123.0 ± 15.2	127.0 ± 22.3
Albumin	23.5 ± 4.2	25.1 ± 2.5
Pre-albumin	0.074 ± 0.027	0.10 ± 0.42
Urinary Nitrogen	-17.5 ± 7.7	-13.6 ± 7.8
Days NPO	4.2 ± 2.7	3.5 ± 1.1

Table 6-4: Baseline Nutritional Status

	TPN	*TEN*
Days to goal	2.1 ± 2.6	3.3 ± 2.6
Avg. caloric intake per kg	21.0 ± 3.6	18.2 ± 5.9
Days on nutrition	11.7 ± 8.6	13.1 ± 10.5
Days to full fluids	12.1 ± 9.0	12.2 ± 9.4
Days to DAT	13.3 ± 9.0	15.0 ± 10.6

Table 6.5: Measures of Nutritional Effectiveness

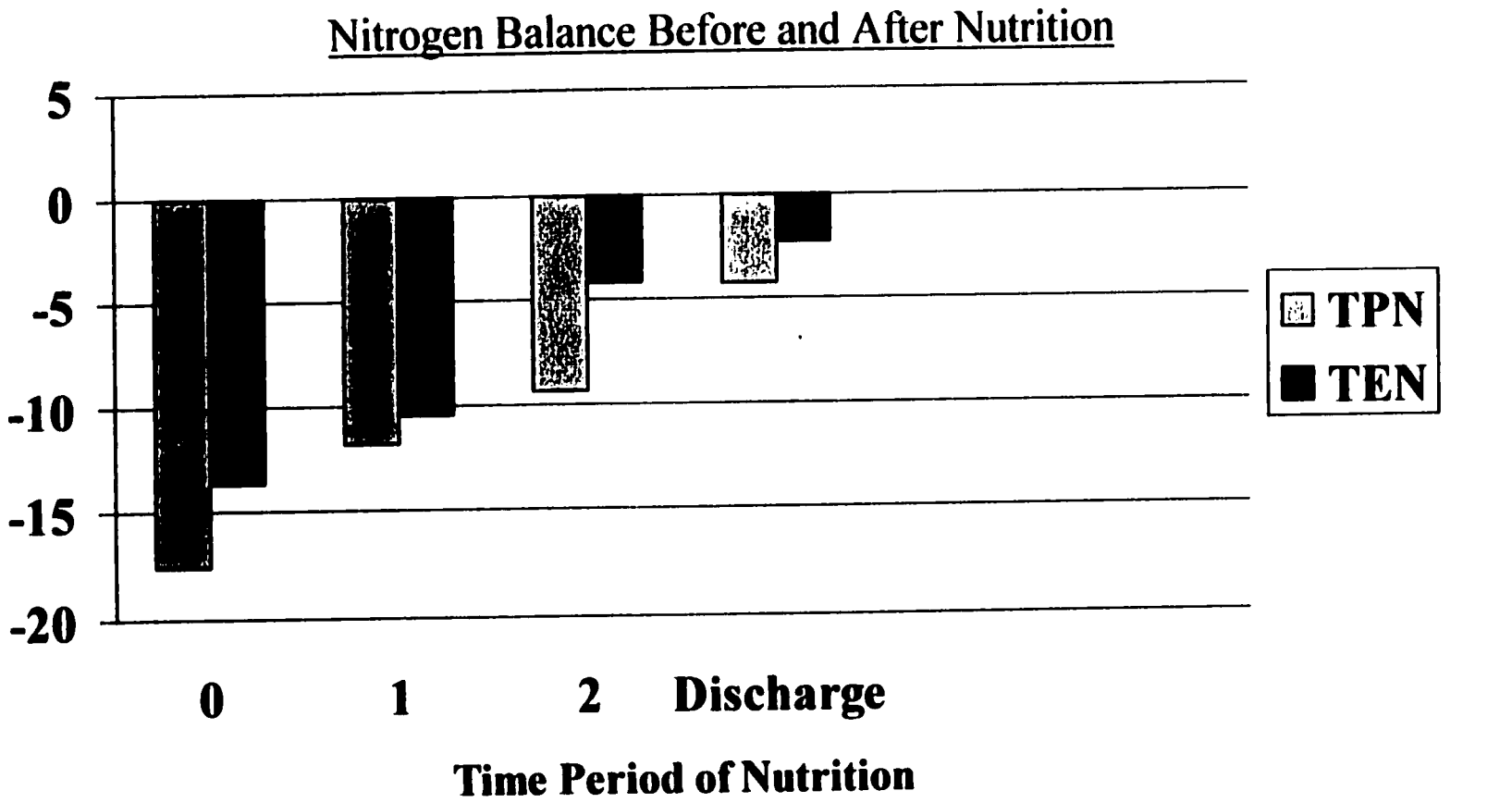

Figure 6-2: 24-hour Urinary Nitrogen Balance

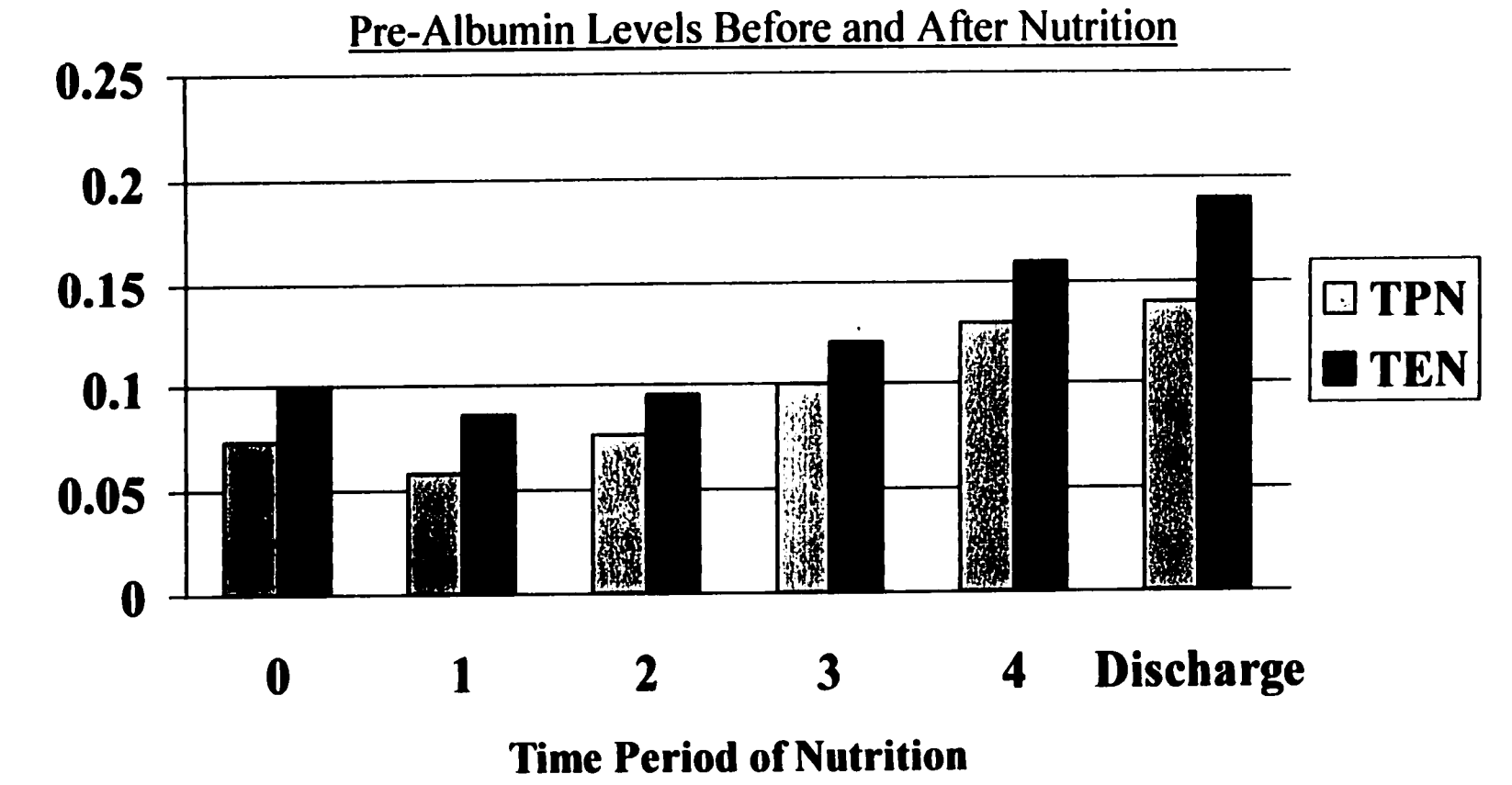

Figure 6-3: Serum Pre-albumin Levels Pre and Post Nutrition

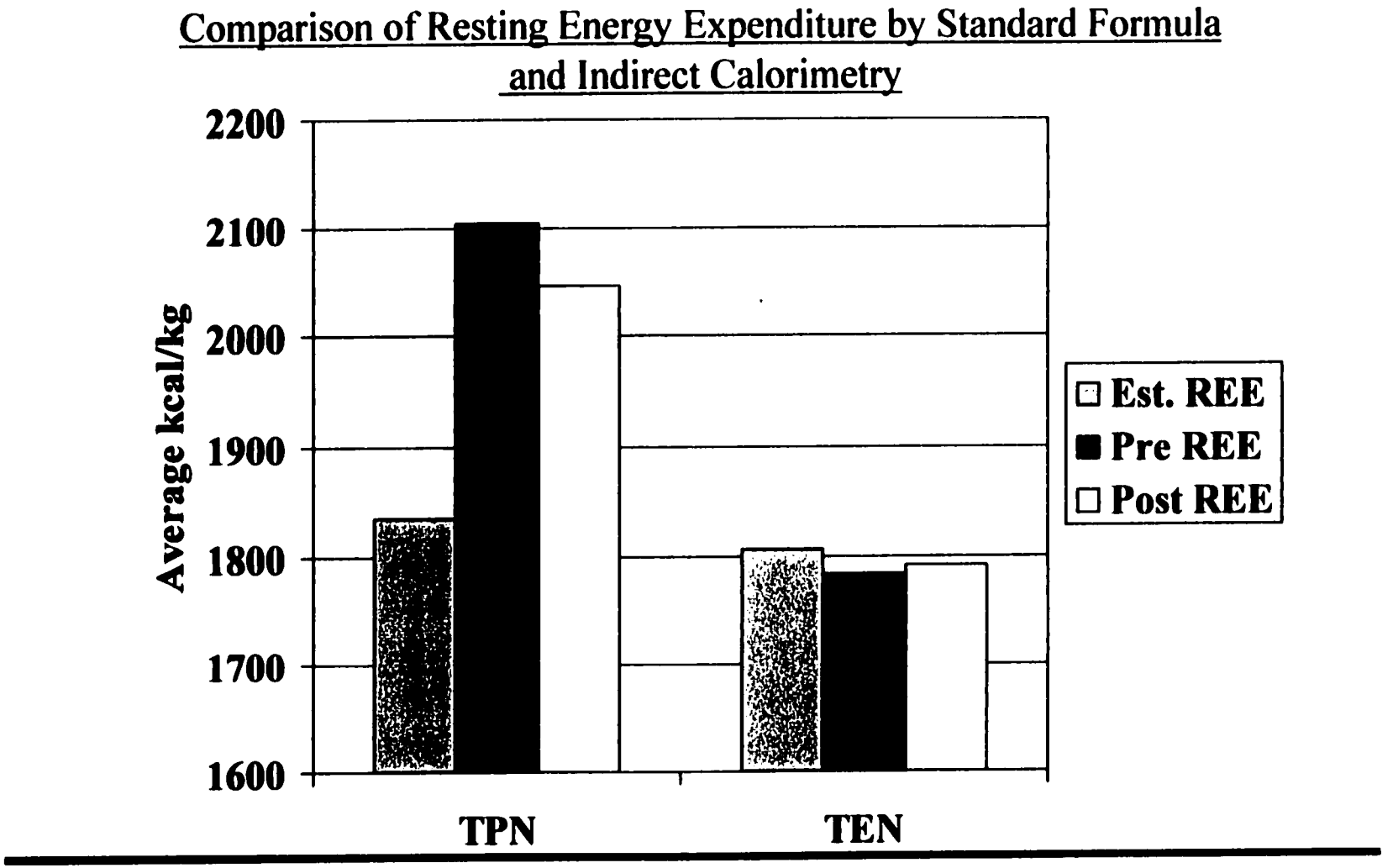

Figure 6-4: Estimation of Resting Energy Expenditure

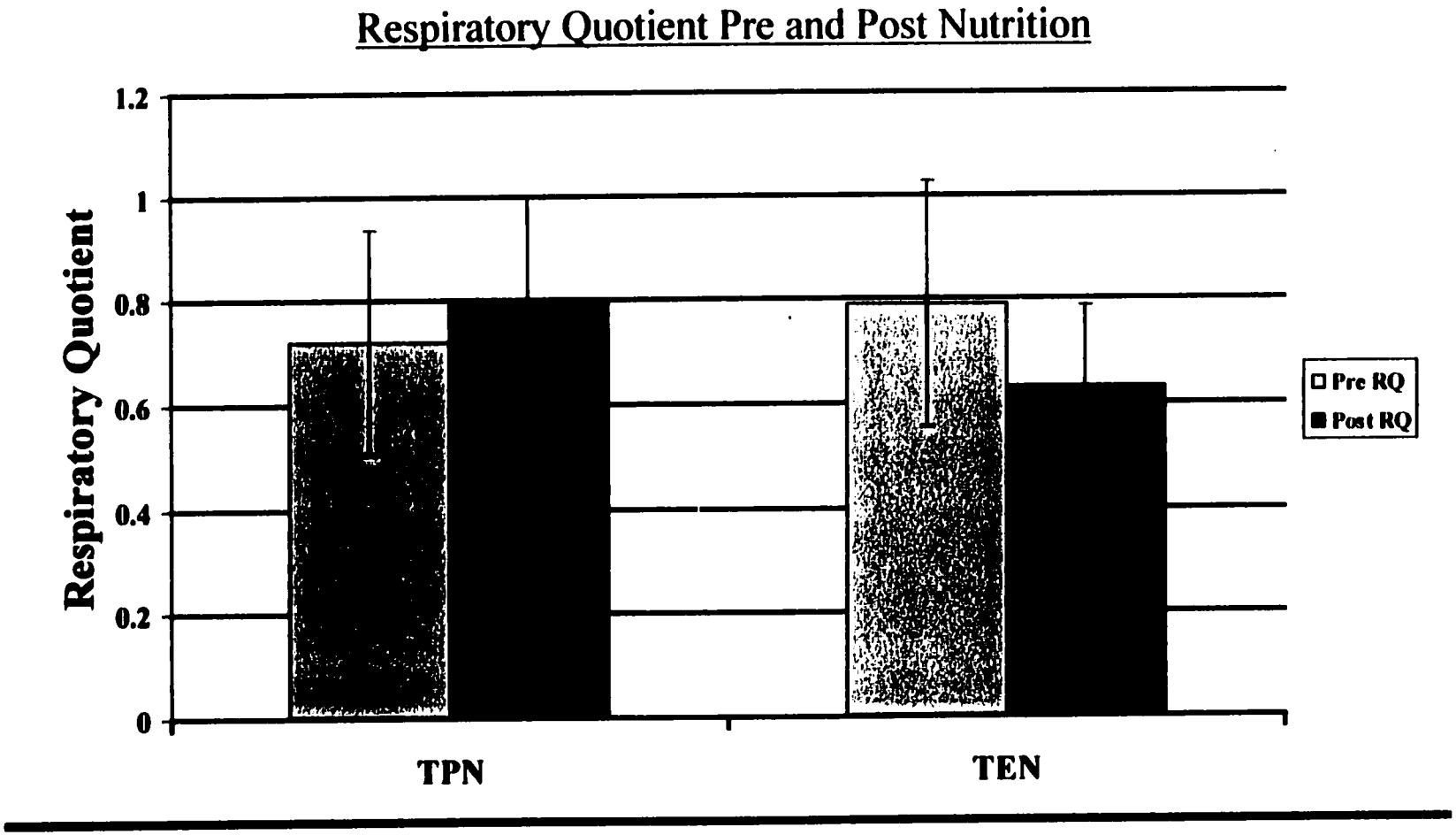

Figure 6-5: Pre and Post Nutrition Respiratory Quotient Levels

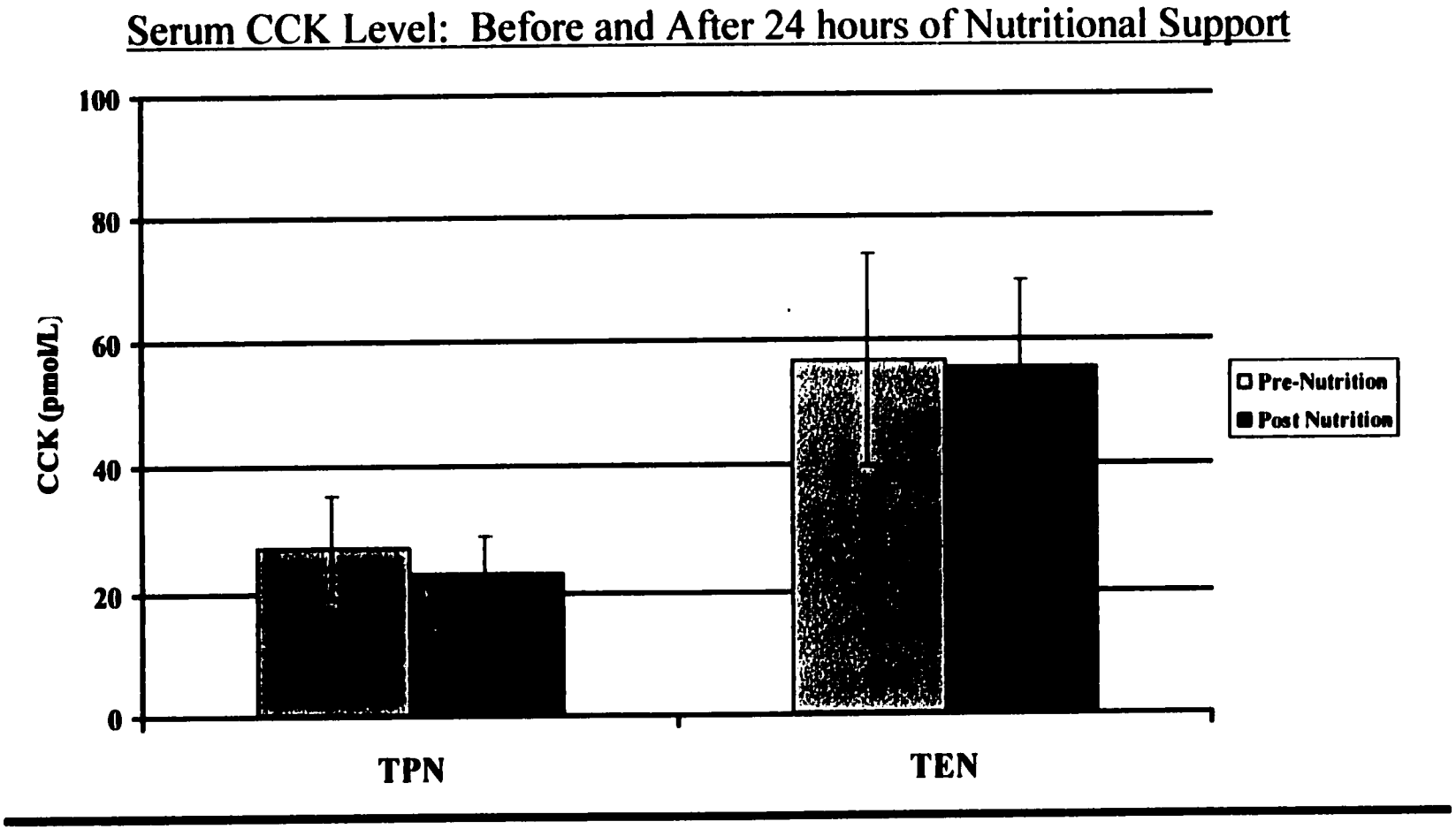

Figure 6-6: Serum Cholecystokinin (CCK) Levels

Pt	Age	Ranson's	APACHE	Etiology	CT Severity
A	66	8	10	Alcohol	C
B	63	6	24	Alcohol	D
C	76	5	21	Gallstones	E

Table 6-6: Mortality

	TPN	*TEN*
Acute Pancreatic Fluid Collections	5	3
Infected Fluid Collections	3	1
Acute Renal Failure	3	2
Acute Respiratory Failure	5	4
Cardiac Failure	1	1
Diabetes	2	1

Table 6-7: Morbidity Related to Pancreatitis

	TPN	*TEN*
PICC Line Hematoma	1	0
Infected Fluid Collection	1	0
Dislodged or Removed NJ Tubes	0	9
Diarrhea	0	5
Gram Negative Bacteremia	0	1
Elevated Blood Glucose	3.6	2.7

Table 6-8: Morbidity Related to Type of Nutrition

Scenario	Cost of TPN	Cost of TEN	ΔCost	p-value
Base	1968.62	1207.83	760.79	0.236
1	1968.62	1086.89	881.73	0.72
2	1968.62	1012.22	956.40	0.042
3	2800.47	1580.92	1219.55	0.072
4	973.94	648.19	325.75	0.365

Table 6-9: Sensitivity Analysis

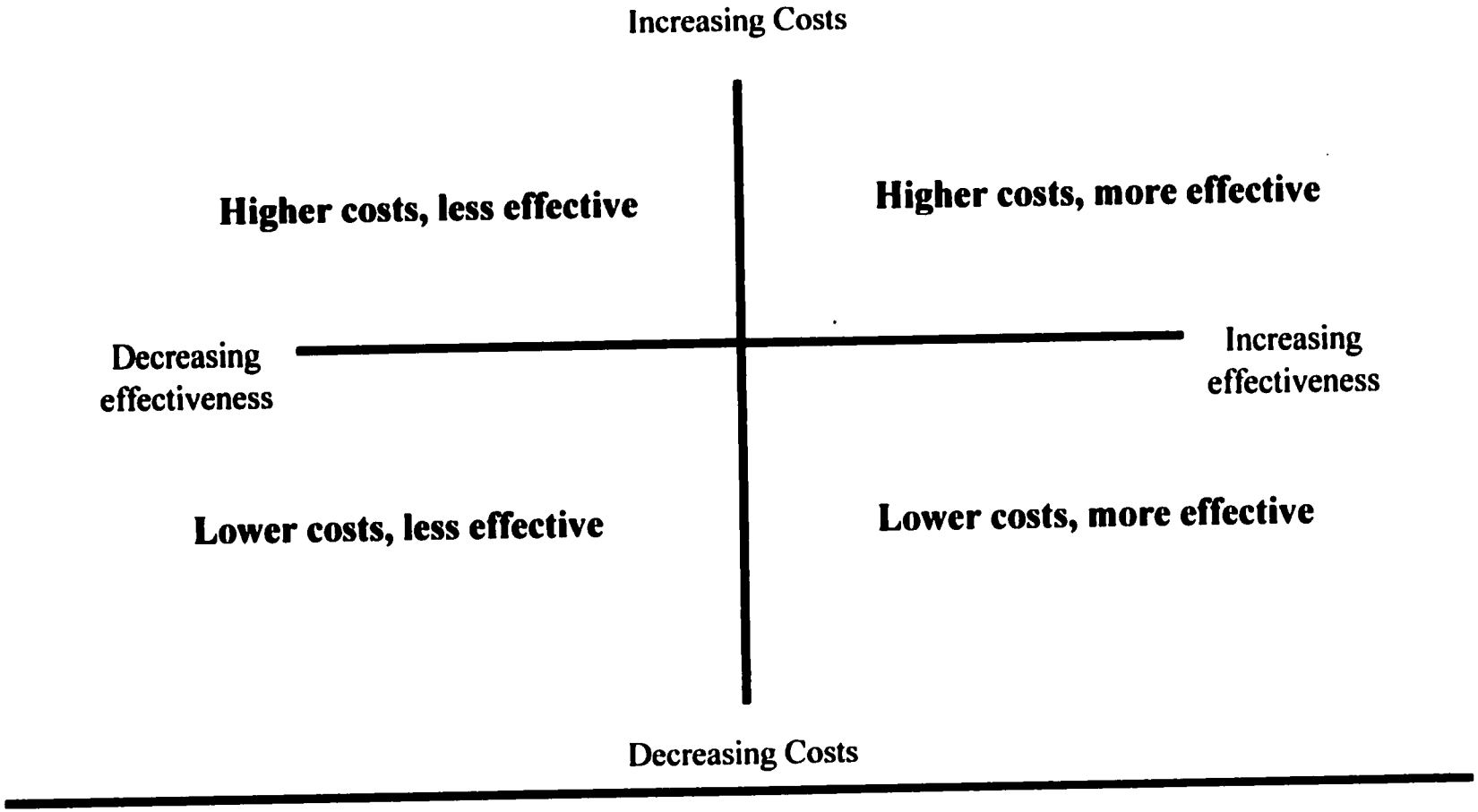

Table 7-10: Interpretation of Cost Effectiveness Ratios
Adapted from Laupacis, A et al. How attractive does a new technology have to be to warrant adoption and utilization. CMAJ. 1992

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Appendix A

COST INVENTORY

COSTING: TOTAL ENTERAL NUTRITION

Costing Event	Description	Cost
1. Peptamen ($/250 mL)	Purchasing price	$4.33
2. Wilson Cook Naso-jejunal Feeding Tube (8 Fr)	Purchasing price	$122.00
3. Direct Procedure Cost	Nursing time, supplies, drugs, preparation and cleaning, and minor overhead	$262.78
4. Physician Fee	Fee Code 01.14 – Non-operative endoscopy Fee Code 58.39B – P.E.J.	$102.89 $89.98
TOTAL	(4.33 * TEN Volume/250) + 577.65	

COSTING: TOTAL PARENTERAL NUTRITION

Costing Event	Description	Cost
1. TPN ($/bag)	Pharmacy cost ($/1000 mL bag) – raw materials, pharmacist and tech time, supplies and tubing	$56.60
2. Groshong Double Lumen PICC Line (5F 77255050)	Purchasing price	$107.00
3. Direct Procedure Costs	Nursing time, supplies, drugs, preparation and cleaning, and minor overhead	$360.91
TOTAL	(55.60 * TPN Volume/1000) + 467.91	

COSTING: NON-NUTRITIONAL COSTS

Costing Event	Description	Cost
1. Daily medical ward cost	Direct nursing time and costs from RAH	$373
Daily surgical ward cost	Direct nursing time and costs from RAH	$488
2. Daily ICU cost	Direct nursing and supply costs from RAH	$1433
3. Computed tomography with interpretation	Operating cost and physicians fee	$288.88
4. Ultrasound examination with interpretation	Operating cost Fee Code – TX222A	$114.64
5. Ultrasound guided drainage		
▫Supplies	Estimated per average procedure	$125.00
▫PIG Tail Catheter	SPD	
ULT8.5-38-25-P-55-DM	Purchasing price	$99.75
ULT10.2-38-25-P-65-MSL	Purchasing price	
▫Physician Fee	Schedule of benefits	$85.60
▫Ultrasound Tech Time	Direct tech time per hour	$40.95

COSTING: OPERATION

Costing Event	Description	Cost
1. Operating Room Time	Case specific nursing time and cost for each study patient undergoing an OR	
2. Surgeon's Fee	Fee Codes: 64.09A – Pancreatitis abscess and drainage 64.43A – 95% Pancreatectomy 64.49 - Other pancreatectomy	 $814.23 $1390.37 $759.31
3. Anesthetist's Fee	Fee Codes: 64.09A – Pancreatitis abscess and drainage 64.43A – 95% Pancreatectomy 64.49 - Other pancreatectomy	 $244.95 $414.46 $229.28
4. Recovery Room Time	Case specific nursing time and cost for each study patient undergoing an OR	
5. ERCP	Cost per ICD-9 CM ERCP Code Fee Code: 64.97A – ERCP 63.86A – Sphincterotomy and papillotomy 63.90B – Stone extraction DI Cost	 $211.64 $84.26 $23.73 $115.97
6. Post Operative Recovery	Length of stay in hospital	