FEEDING PRACTICES IN OPEN ABDOMEN FOLLOWING LAPAROTOMY: AN ASSESSMENT OF NUTRITION ADEQUACY AND CLINICAL OUTCOMES

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ABSTRACT

Proper nutrition can promote healing and improve clinical outcome. Open abdomen patients are at risk of declining nutritional status. To investigate this issue, we first assessed nutrition adequacy and clinical outcomes by using data from a retrospective study on 33 patients. We assessed potential factors as correlates of altering resting energy expenditure by using data from a prospective pilot study of 7 open abdomen patients, after implementing indirect calorimetry as a standard of care at a Level-1 trauma center in Montreal. At baseline, the vast majority of the participants were underfed in the first study, while in the second study unexpected dynamic changes in resting energy expenditure were observed after closure of the abdomen compared to before closure of the abdomen. The findings of this research highlight the need for large multi-center studies in order to better understand nutritional targets and nutritional risks for open abdomen patients.

ABRÉGÉ

Une bonne nutrition peut favoriser la guérison et améliorer les résultats cliniques. Les patients à abdomen ouvert risquent une dégradation de leur état nutritionnel. Pour étudier cette question, nous avons d'abord évalué le niveau de suffisance nutritionnel et les résultats cliniques en utilisant les données d'une étude rétrospective portant sur 33 patients. Après avoir mis en œuvre la calorimétrie indirecte comme norme de soins dans un centre de traumatisme de niveau 1 à Montréal, nous avons évalué des facteurs potentiels comme corrélats de dépense énergétique au repos en modification à l'aide de données provenant d'une étude pilote prospective de 7 patients à abdomen ouvert. À la base, la grande majorité des participants étaient sous-alimentés dans la première étude, tandis que dans la seconde étude des changements dynamiques inattendus au niveau de la DER ont été observés après la fermeture de l'abdomen. Les résultats de cette recherche soulignent la nécessité pour de grandes études multicentriques afin de mieux comprendre les objectifs nutritionnels et les risques nutritionnels pour les patients à abdomen ouvert.

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AUTHOR CONTRIBUTIONS

Muhamad Mamdouh Elhusseini Hassan wrote this thesis and was the principal author both of the manuscripts included in this thesis. For both manuscripts, Muhamad was directly involved in the study design, data collection, analysis and interpretation of data, and drafting of the manuscripts. Kosar Khwaja was the primary thesis supervisor and the primary investigator of the research study and reviewed the thesis. Sameena Iqbal is co-author on both papers, and contributed greatly in every step of the research process in term of data collection, statistics and data analysis. Mostafa Alhabboubi was involved in data collection and interpretation of the data. Lyne St-Laurent and Eleanor Eckert were involved with the review of the data. The remaining co-authors (Dan Deckelbaum, Tarek Razek, for manuscript A; and Nancy Fong, Jeremy Grushka, Dan Deckelbaum, Tarek Razek, for manuscript B) made substantial contributions to interpretation of data and review of the manuscripts. Evan Wong is a co-author on the survey. He was involved on editing and reviewing the survey.

LIST OF ABBREVIATIONS

WHO = World Health Organization

T.A.C = Trauma Association of Canada

A.A.S.T = American Association for the Surgery of Trauma

A.S.P.E.N = American society of enteral and parenteral nutrition

ACS = Abdominal Compartment Syndrome

I.A.P = Intra-abdominal pressure

DC =Damage Control

OA= Open abdomen

EN = Enteral nutrition

TPN = Total parenteral nutrition

IC = Indirect calorimetry

REE = Resting energy expenditure

TEE=Total energy expenditure

BMR = Basal metabolic rate

PEEP = Positive end-expiratory pressure

FiO2 = Fraction of inspired oxygen

VE = Minute of ventilation

RQ = Respiratory quotient

Tmax = Maximum temperature

SD = Standard deviation

1. INTRODUCTION

Optimizing nutrition therapy is a potential avenue for improving clinical outcomes in critically ill patients. In the intensive care unit (ICU), the relationship between optimized energy requirements and reduced morbidity and mortality is controversial. However, studies from both surgical and medical settings have shown patients to be insufficiently fed during their ICU stay when compared with described targets, which may subsequently affect both health and patient-based outcomes.[1-3]

Although the open abdomen technique is associated with favourable outcomes following laparotomy, limited data exist on nutrient adequacy and the risk of inadequate nutritional intake. In addition, despite the effects of hypermetabolism and hypercatabolism in injured patients being well documented, the provision of optimal nutrition support to patients with an open abdomen is complex due to alternations in metabolism. Therefore, it has become necessary to scale nutritional need with optimum targets to overcome the unparalleled feeding challenges that face open abdomen patients during the recovery phase in the ICU.

Accordingly, the purpose of this study is to assess the differences in nutrient intake and adequacy among open abdomen patients. Furthermore, the study looks at the potential factors associated with changes in resting energy expenditure.

2. LITERATURE REVIEW

2.1 TRAUMA AND OPEN ABDOMEN STATISTICS

Trauma is one of the leading causes of death in both developed and developing countries. As a result, injuries represent a growing burden for health care and the economy worldwide.[4, 5] In particular, abdominal traumas have approached a mortality range between 10% and 30%.[6]

In North America, and particularly in Canada, injuries are the leading cause of death during the first four decades of life.[7] Moreover, trauma injuries account for 30% of all life-years lost in the United States. Because trauma is a health issue that affects people of all ages, its impact on life years lost is equal to the life years lost from cancer, heart disease, and HIV combined, where cancer accounts for 16% and heart disease accounts for 12%.[8] Furthermore, in 2010, the World Health Organization (WHO) reported that significant increases in injuries up to 2020 are expected, owing to increased injury-related deaths, particularly those which are violence and war-related, as well as self-inflicted and road traffic injuries.[9]

Within the context of open abdomen patients, use of the open abdomen approach has increased in recent years, but the actual prevalence is still undefined. However, Teixeira et al. documented that 10% of trauma laparotomies are managed with damage control laparotomy, and this technique requires an open abdomen approach over a 3-year period.[10]

A survey among 102 members, conducted by Kirkpatrick et al.[11] with responses rate of 83% found that 90% (70/78) of participants reported used an open abdomen approach after a trauma laparotomy, with a trend ($p = 0.09$) toward a greater number of laparotomies in big centers when compared to smaller centers.

In 2008, another survey conducted by MacLean et al.[12] was answered by 103 members of the American Association for the Surgery of Trauma (A.A.S.T), in response to questions about managing patients with open abdomens. The results of this survey revealed that 74% of surgeons felt that the number of cases had increased each year, while 5% thought it had decreased, with 19% stating that it had not changed.

2.2 DAMAGE CONTROL SURGERY AND OPEN ABDOMEN TECHNIQUE

2.2.1 OVERVIEW

Over the last seven decades, the open abdomen technique and damage control concept has been used as a life-saving technique for both blunt and penetrating traumas and general surgical emergencies. In particular, Ogilvie et al.[4] have reported that, throughout the 19th and first part of the 20th centuries, the open abdomen technique was used in military settings during World War II. The concept of open abdomen has also been studied by Lucas and Ledgerwood[13], Stone and Lamb[14], and Stone et al.[15], who described the first damage control procedure, performed on a patient who developed coagulopathy during a laparotomy performed in a liver trauma setting in the early 1980s.

In 1993, the damage control laparotomy approach, also called an "abbreviated laparotomy," was first studied by Rotondo et al.[16], who wrote: "Damage control (DC) as initial control of hemorrhage and contamination followed by intraperitoneal packing and rapid closure, allows for resuscitation to normal physiology in the intensive care unit and subsequent definitive re-exploration." Moreover, Rotondo et al. explored the efficacy of this concept in compression with definitive laparotomy (DL). No significant differences were identified between 22 DL and 24 DC patients and found that actual survival rates were similar (55% DC vs. 58% DL). As a result, they concluded that the damage control concept is a promising approach for increasing survival in unstable trauma patients with major vascular and multiple penetrating abdominal injuries. Since then, others have reported the efficacy of using this technique as part of the damage control concept.

Despite the lack of strong evidence to prove this technique is associated with improved mortality and other positive outcomes, several studies have showed unexpected survival rates.(10, 17, 18) For instance, in 2001, Johnson et al.(19) looked at groups that had undergone DC surgery, comparing those from his study with those treated a decade earlier (HS). He found that the survival rate was significantly higher in the study group compared with the HS group (90% vs. 58%; P= 0.02). Moreover, Finlay et al.(20) studied prospectively the impact of damage control surgery on survival rates in non-trauma patients over a 2-year period. They concluded that the observed mortality rate of 7·1 % of patients (1/14) was lower than that predicted, and this may be attributable to the use of DC principles at initial surgery in the non-trauma setting.

Another study conducted by Sutton et al.(17) examined the validity of damage control laparotomy on long-term morbidity by calculating the survival rates of 56 trauma patients over a 20-month period. Findings showed that overall mortality was estimated at 27% and 0% during the first admission and required readmission, respectively. Nevertheless, he found that damage control laparotomy is associated with significant complications, such as bacteremia and fistula, with a high readmission rate (31 out of 41) most often for infectious complications.

Moreover, Teixeira et al.(10) and colleagues published their experiences with the open abdomen technique, reporting on over 900 laparotomies during a 3-year period. Researchers found that out of 900 laparotomies, 93 (10%) were left open and 91% of patients survived for definite abdominal closure. Their results showed that fascial closure was achieved in 72 patients (85%) on average, over 3.9 ± 3.7 days. Of the remaining 13 patients, seven were closed with mesh, five by skin grafting, and one had skin-only closure, and complications such as entero-atmospheric fistulas occurred in 14 (15%) patients.

Lastly, in 2010, Waibel et al. and Rotondo et al.[21] summarized the indications for using damage control (DC) as follows:

1. Hemodynamic instability
2. Coagulopathy on presentation or during operation (clinical or laboratory)
3. Severe metabolic acidosis (pH < 7.2 or base deficit > 8)
4. Hypothermia on presentation (< 35°C)
5. Prohibitive operative time required to repair injuries (> 90 mins)
6. High-injury blunt torso trauma
7. Multiple penetrating torso injuries
8. Multiple visceral injuries with major vascular trauma
9. Multiple injuries across body cavities
10. Massive transfusion requirements (> 10 units packed red blood cells)
11. Presence of injuries better treated with nonsurgical adjuncts

2.2.2 INDICATIONS OF OPEN ABDOMEN

In the modern era of the open abdomen approach, the main indications for use of this approach in trauma and non-trauma settings have been reported in numerous articles.[21-24]

Diaz et al.,[23] in collaboration with the chair, vice chair of the Eastern Association for the

Surgery of Trauma (E.A.S.T), and a group of 18 surgeons, summarized the literature during the period of 1984 through 2009 to establish guidelines regarding the use of open abdomen for both trauma and general surgery emergencies.

In this structured literature review, Diaz et al.[(23)] and his group aimed to guide surgeons regarding the indications and early management of the open abdomen technique in both trauma and non-trauma surgery, including the nutritional aspect, which will be discussed later in this thesis. They summarized the indications for the open abdomen technique into four major indications, encompassing (from Tables 1 and 2 of the appendices):

1. Abdominal Compartment Syndrome (ACS)
2. Damage Control (DC)
3. Emergency general surgeries
4. Vascular surgery such as ruptured Abdominal Aortic Aneurysm (rAAA)

In this review by Diaz et al.,[(23)] only prospective and retrospective articles related to open abdomen management in adult participants were included. Any case reports, reviews, letters, commentaries, editorials, and articles focusing only on pediatric participants were excluded. Ninety-five articles were reviewed to develop practical guidelines and clinical recommendations. Moreover, Diaz et al. have highlighted these recommendations regarding clinical indications for the open abdomen technique based on the levels of recommendations, as shown in Tables 1, 2, and 3 (see the appendices).

A western trauma association study was conducted by Burlew et al.[(25)] on 597 patients requiring an open abdomen after trauma over seven years in 11 trauma centers. The data revealed that out of 597 open abdomen patients, 548 (92%) had an open abdomen due to a damage control operation, whereas the remainder, 8% (49/597), had experienced an abdominal compartment syndrome.

In the same context, in 2013, the World Society of the Abdominal Compartment Syndrome (WSACS)[26] updated the definition and risk factors of ACS and the open abdomen technique. WSACS has also made new recommendations and suggestions regarding the management of ACS based on open abdomen classifications (Table 1).[26, 27]

As per these suggestions, patients undergoing a laparotomy after trauma who are suffering from physiologic exhaustion should be treated with the prophylactic use of the open abdomen versus closure and expectant Intra-abdominal pressure (IAP) management (New Management Suggestion 9 [GRADE 2D]). However, in GRADE 2B, WSACS suggests that physicians *not* routinely utilize the open abdomen approach for patients with severe intra-peritoneal contamination who are undergoing emergency laparotomy for intra-abdominal sepsis, unless Intra-abdominal hypertension (IAH) is a specific concern (New Management Suggestion 10).

Table 1 – Open abdomen classification by the World Society of the Abdominal Compartment Syndrome (WSACS)

Grade	Description
1	No fixation 1A Clean, no fixation 1B Contaminated, no fixation 1C Enteric leak, no fixation
2	Developing fixation 2A Clean, developing fixation 2B Contaminated, developing fixation 2C Enteric leak, developing fixation
3	Frozen abdomen

	3A Clean, frozen abdomen 3B Contaminated, frozen abdomen
4	Established enteroatmospheric fistula

2.2.3 CHALLENGES ASSOCIATED WITH OPEN ABDOMEN

Open abdomen approach advances have allowed significant improvements in overall survival.[17, 19, 20] Nevertheless, short and long term complications remain the most challenging part of managing patients with open abdomens.[17, 28] There have been several reports aiming to elucidate the challenges that enhance adverse outcomes of using the open abdomen technique.

Miller et al.[28] and colleagues reported their experiences with 344 open abdomen patients, and concluded that morbidity associated with wound infection in these patients was estimated as high as 25%. They also reported that complications increased significantly after 8 days ($p < 0.0001$), from the initial operative laparotomy to the fascial closure of the abdominal cavity.

Moreover, challenges associated with open abdomen have been discussed in many articles [17, 24, 26, 29-33] including:

1. Fluid and protein loss and negative nitrogen balance[29, 31]
2. Malnutrition and fluid and electrolyte imbalance[24] [30, 31, 34]
3. Enteroatmospheric fistulas[30, 33, 35]
4. Loss of abdominal wall domain
5. Intra-abdominal infection and sepsis[32]
6. Prolonged intensive care unit and hospital stay[36]
7. Increased edema will lead to increased intra-abdominal pressure will lead to ACS[24, 37]
8. Readmission[17]

9. Increased hospital costs[36, 38]

Although implementation of the open abdomen approach in trauma and general surgery emergencies is associated with numerous challenges, as outlined above, this thesis will focus on the nutritional challenges with respect to open abdomens

Due to massive resuscitation with blood products, medications, and fluids transfusion, which subsequently lead to massive abdominal edema and significant amounts of retained fluids, delayed closure of the abdomen is becoming a problematic issue.[24, 39] The delayed closure of the abdomen prolongs the patient's stay in hospital and the ICU, and can result in necessary readmission for abdominal wall reconstruction.[17, 24] Furthermore, a large open wound such as an open abdomen associated with trauma and surgery, enhances the stress and hyper-catabolic state.[40, 41]

The presence of this vicious cycle in open abdomen patients could lead to unfavourable nutritional outcomes, such as a negative nitrogen balance as a result of the loss of fluid and protein from the peritoneal cavity. Thus, achieving abdominal closure within the first week after the initial damage control surgery operation remains a major goal in the surgical management of these patients.

In the context of nutrition, the ideal route and start time of feeding and the optimal supply of calories and protein, as well as the assessment of the energy requirements all together, make optimizing nutrition therapy in the open abdomen population a phenomenal challenge.

Another challenging issue observed in the open abdomen approach might be due to sedation and analgesia, and neuromuscular blocker are frequency used and can be taken to decrease IAP.

2.3 NUTRITION PRACTICES IN OPEN ABDOMEN

2.3.1 ENTERAL FEEDING

The benefits of early nutritional management for injured patients have been addressed broadly over many decades.[42-47] However, there has remained a great degree of heterogeneity in the literature discussing nutritional practices in patients with an OA. In addition, the idea of early enteral nutrition in the management of the OA is relatively conflicting and poorly investigated. There are currently no universally agreed upon guidelines regarding nutrition for open abdomen patient.

2.3.1.1 TOLERANCE AND CLINICAL OUTCOMES

In this context, a retrospective chart review was performed by Tsuei et al.[48] over 3.5 years on 45 open abdomen patients aiming to evaluate the tolerance of enteral nutrition (EN). Patients were included in the evaluation only if they received at least four consecutive days of enteral feeding. Intolerance was defined as watery diarrhea (volume $\geq$ 500 mL/d) on at least two consecutive days, gastric reflux, and/or severe abdomen distention.

Of 45 the open abdomen patients, 28 were excluded due to receiving $<$ 4 consecutive days of EN, leaving 14 patients for analysis. These 14 patients received a total of 267 days of enteral nutrition, with periods ranging from 4 to 35 consecutive days (on average, 19.1 $\pm$ 12.3 days). Intolerance to EN as defined above was documented in 9 (64%) patients, diarrhea and gastric reflux occurred in 42% (n=6) and 36% (n=5) of patients, respectively. However, no clinical findings suggestive of aspiration of enteral feeds were found in any patient.

This descriptive study shows that, despite there being such wide variability in the duration of enteral feeding, EN can be effectively used in open abdomen patients after laparotomy, as 57% of the patients (8/14) reached at least 80% of predicted or measured energy expenditure. Overall, it appears that open abdomen patients tolerate EN relatively well, and thus may not need total parenteral nutrition (TPN).

A subsequent descriptive study by Cothren et al.[(49)] also examined enteral feeding in 37 patients with abdominal compartment syndrome (ACS) over a 7-year period. During the study, enteral feeding was never started in 12 patients, 4 died within 48 hours of admission, 7 required vasoactive products until their death, and one patient developed an enterocutaneous fistula and required parenteral nutrition. Among the 25 patients where feeding was initiated, 13 had feeds started within 24 hours of abdominal closure, while 5 patients were fed with open abdomens and 7 had a delay after fascial closure because of vasopressors, increased abdominal pressure, and multiple operations (foremost, orthopedic procedures).

A published Chinese abstract by Wang et al.[(50)] reported results of EN being administrated in 21 open abdomen patients. Intolerance involving diarrhea, gastric reflux, vomiting, and abdominal distention occurred in 67%, 23%, 9.5%, and 23% of the patients, respectively. EN was started in these open abdomen patients on an average of 8.8 ± 5.5 days, and lasted to an average of 51.5 ± 33.6 days.

In contrast, in 2014, Yin et al.[(35)] conducted a retrospective descriptive study involving 9 open abdomen patients with enteroatmospheric fistulae. EN was established in all 9 patients after they had developed the enteroatmospheric fistulae; only 44% (4/9) of the patients received EN before the fistulae occurred. With regard to adverse effects of enteral feeding, the incidence of feeding intolerance was 55.6%, and the occurrence of complications related to feeding was 11%. Considering this, PN was administered in all patients before the initiation of EN, and was hold when one-half to two-thirds of targeted EN was achieved.

2.3.1.2 CLINICAL OUTCOMES

Early Enteral Nutrition (EEN) support in open abdomen patients was described by Collier et al.,[38] who conducted a retrospective study on 78 open abdomen patients, over the first 14 days of admission postoperatively. He concluded that early enteral feeding (n = 43) begun in less than 4 days in comparison with late enteral feeding (n = 35) may result in higher primary fascial closure (74 % vs. 49 %; p = 0.02), lower fistula rate (9 % vs. 26 %; p = 0.05), and lower total hospital charges (172,283 ± 188$ vs. 223,349 ± 138$; P = 0.04, respectively). Collier et al. also documented that 15 patients did not have any enteral nutrition initiated within the 14-day data-collection period. Overall, he concluded that early enteral nutrition in open abdomen patients is safe and may be associated with improved outcomes such as earlier abdominal closure, decreased fistula rates, and decreased hospital costs.

Additionally, Dissanaike et al.[43] explored the effects of early enteral feeding on 32 open abdomen patients within 36 hours in comparison with a non-immediate feeding group (n=68). It was reported in this prospective multi-centre cohort study that early feeding in open abdomen patients with an intact GI tract is safe and may be associated with reduced nosocomial infections, mostly pneumonia episodes (p=0.008). However, they reported no significant difference in early abdominal closure, occurrence of multi-organ dysfunction syndrome, length of ventilator days, ICU days, or hospital days, or in mortality.

Similarly, Byrnes et al.[51] evaluated feasibility and the impact of using EN in obtaining facial closure in 23 open abdomen patients. The data showed that enteral feeding was successfully initiated in 52% of the open abdomen patients prior to closure of the abdomen. This was performed by 3.8 days on average after initial laparotomy. After dividing 23 patients into two groups (12 vs. 11 patients) based on initiation of enteral nutrition as well as timing to fascial closure, the time of fascial closure after initial laparotomy was significantly longer in the group that received enteral nutrition before fascial closure compared to the group that did not receive enteral nutrition before fascial closure: (7.03 vs 3.4 days; p = 0.003, respectively). In terms of other outcomes, no significant difference was found between the two groups in term of mortality, pneumonia (p = 0.59), fistula formation, and timing of enteral nutrition (p = 0.73).

Furthermore, Yuan et al.(52) reported improved fascial closure rate in 36 open abdomen patients with enterocutaneous fistula who were fed within 14 days (8.3 ± 3.8 days) (142.8 vs. 184.5 days; P = 0.017), with decreased mortality (11.1% vs. 47.8%; P < 0.001), as opposed to 46 open abdomen patients who did not start EN within 14 days (29.9 ± 20.9 days). However, the initiation time of Parenteral Nutrition (PN) was similar (1.0 ± 7.1 vs. 1.6 ± 9.2 days; P = 0.642). While, the duration of PN was significantly prolonged among patients with delayed initiation of EN compared with those fed within 14 days.

Lastly, a large multi-center study conducted by Burlew et al.(25) reviewed the data of 11 trauma centers from the Western Trauma Association over a 7-year period. The aim was to evaluate the role of EN in open abdomen patients with or without enteric injury after trauma and its impact on closure rates and nosocomial infections. In the study period, by 3.6 ± 1.2 days on average after laparotomy, out of 597 patients, enteral nutrition was successfully initiated in 230 patients (39%). However, EN was started in 72 open abdomen patients with bowel injuries.

First, Burlew et al.[25] compared all open abdomen patients who received EN with those who remained nil per os (NPO). The rates of total parenteral nutrition (TPN) supplementations were similar between the two groups (21% vs. 23%; p = 0.56). The abdomen was closed at the second surgical exploration in 26% of those who received EN, and 26% compared to 54% of those were not fed enterally. Ultimate fascial closure was significantly higher in those patients receiving EN (75% vs. 67%; p = 0.03), but the time to final closure was significantly longer in the EN group compared with the NPO group (9 vs. 5 days; p = <0.0001). Moreover, pneumonia episodes were significantly higher with EN compared to NPO (43% vs 33%; p = 0.01). However, overall mortality rate was significantly lower with EN compared to NPO (9% vs 17%; p = 0.006) knowing that significantly fewer patients with bowel injuries were started on EN compared to the NPO group (32% vs. 59%; p = >0.001).

Secondly, Burlew et al. performed subgroup analysis on patients with and without bowel injury (290 and 307, respectively) before the first attempt at closure. In the 307 patients without bowel injury, the ultimate fascial closure rate was significantly higher with EN (n=156) compared to NPO (n=151) (84% vs. 50%; p = < 0.0001), but had a significantly longer duration (6.6 vs. 3.6 days; p = <0.0001, respectively). Moreover, the mortality rate was significantly lower in the EN compared to NPO group (10% vs. 23%; p = 0.004), respectively. No significant difference was found between the two groups in adjunctive Total Parenteral Nutrition (TPN) rate (10% vs. 17%; p = 0.07), in complications such as pneumonia episodes (46% vs. 38%; p = 0.14), or in outcomes such as percentage of ICU-free days and ventilator-free days. Further, logistic regression revealed that there was an independent association between EN and successful fascial closure (OR, 5.3; p < 0.01). In addition, a significant association between EN and decreased complications (OR, 0.46; p = 0.02) and decreased mortality (OR, 0.30; p = 0.01) rates were also identified.

In contrast, in the 290 patients with bowel injury, the ultimate fascial closure rate was significantly lower in the EN (n=74) compared to NPO (n=216) group (55% vs. 78%; p = 0.0001), with a significant shorter duration in the NPO group (4.8 vs. 13 days; p > 0.0001). No significant difference was found between the two groups in outcomes such as mortality, percentage of ICU-free days and ventilator-free days, or pneumonia episodes. The only significant complications found were abdominal complications (such as intra-abdominal abscess, anastomotic leaks, enterocutaneous fistula, or fascial dehiscence) in the EN group compared to the NPO group (45% vs 30%; p = 0.02, respectively). Notably, an adjunctive TPN rate was higher in the same groups (45% vs. 27%; p = 0.006), respectively. In term of logistic regression analysis, there were no significant associations between fascial closure and EN (OR 0.6, p=0.2), complication rates and EN (OR 1.7, p=0.19), and mortality and EN (OR 0.79, p=0.69).

Lastly, after excluding the 245 patients who closed after the second attempt closure, subgroup analysis was performed on 320 open abdomen patients. Of these 320 patients, 151 had no bowel injury while 169 patients had bowel injury. In the bowel injury group (n=169), EN had been administrated in 64 patients (38%). The definitive rate of closure was significantly lower in the EN compared to NPO group (55% vs. 71%; p =0.03), significantly longer period (14 vs. 7 days; p < 0.0001). Moreover, no significant difference was found between the two groups in terms of adjunctive TPN administration rates, complications, or outcomes such as mortality.

In comparing EN in those without bowel injury (n= 93) with the NPO group (n= 58), it was found that in the EN group, patients had significantly lower adjunctive TPN rates (12% vs. 33%; p = 0.003) with significantly higher definitive fascial closure rate was in the same group

(79% vs. 45%; $p < 0.001$). No significant results were found between the two groups in terms of demographics data, complications, or outcomes. He concluded that EN was associated with higher fascial closure rate and lower complication and mortality rate for patients without bowel injury. However, for those with bowel injury EN not seem to affect closure rate, complication and mortality rate.

2.3.2 PARENTERAL NUTRITION

Multiple studies have demonstrated the superiority of enteral nutrition compared to parenteral nutrition in critical illness.[39, 47, 53-58] To date, despite the surge in studies regarding EN, there is no sufficient documented data that shows clear benefits of PN or contraindications in the use of early enteral nutrition (EEN) in the open abdomen setting.[39]

Moreover, no studies have obviously reported adverse events with the use of EN prior to fascial closure. The evidence is not definitive regarding the benefits of using PN as an alternative route of feeding. Parenteral Nutrition, however, has been shown to play a valuable role as a supplement or as an adjunctive to EN when EN has not been feasible.[23, 25, 31, 34, 35, 43, 48, 55, 59]

In a review on open abdomen management, Diaz at al.[23] noted that TPN should be considered for open abdomen patients with abdominal pain, distension, increased nasogastric drainage, or any signs of intestinal ileus.[60]

In two reviews by Powell et al.[31] and Friese et al.[30], it was demonstrated that in well-nourished patients, it has not been proven that combining EN and PN is superior to EN alone. Furthermore, when feeding an open abdomen patient, it is considerable to delay PN use except when enteral feeding is not tolerated for prolonged periods (7–10 days), if the patient was malnourished prior to the use of an open abdomen approach, or if there is a severe fistulous.[30, 31]

2.3.3 NUTRITIONAL ADEQUACY IN OPEN ABDOMEN

Nutrition management for surgical patients aims to provide energy and promote wound healing and resistance to infection while preventing the loss of body proteins.[61] In open abdomen patients, the concept of monitoring nutritional adequacy remains a poorly studied area. To date, only a few small studies have been conducted to evaluate nutritional adequacy in the open abdomen population.

In 2003, Tsuei et al.[48] studied the effectiveness of enteral nutrition in terms of tolerance and achieving prescribed targets in 14 patients, all of who had an open abdomen and EN for a minimum of 4 consecutive days over 3.5 years. The efficacy of EN was defined as the ability to feed the patient to at least 80% of the estimated energy target. The caloric target was either predicted by using the Harris-Benedict equation or was measured by indirect calorimetry, while protein need was estimated using an average range of 1.4 to 1.6 g/kg per day. To begin, researchers calculated the average daily caloric or protein intake by multiplying the average daily caloric or protein intake by days of received EN. The results revealed that the average daily total caloric intake was 77% ± 27% of estimated values, with a range of 39% to 127% for all participants. Moreover, the average daily protein intake was 68% ± 24% of estimated needs, with a range of 37% to 105% for all participants. Fifty-seven percent (8/14) patients achieved at least 80% of the estimated caloric target.

Collier et al.[38] found that when enteral nutrition was provided over 14 postoperative days for 78 patients, only 2 patients (3%) had enteral nutrition provided on postoperative day 1, while 88% had no nutrition provided, either enterally or parenterally. On postoperative day 7, the mean percent goal met for enteral nutrition was 54% for 53% (n=41) of the patients, while on postoperative day 14, the mean percent goal met for enteral nutrition was 74% for only 29% (n=23) of the patients. Researchers also stated that the enteral feedings may have been supplemented with PN.

Dissanaike et al.[43] explored the effects of early enteral feeding on 32 open abdomen patients within 36 hours in comparison with a non-immediate feeding group (n=68). In terms of nutritional parameters, the total enteral calories delivered to the immediate feeding group were on average 377.7 ± 64.57 kcal during the first 48 hours. However, the non-immediate feeding group received only 1.6 ± 1.2 kcal. On the other hand, no significant difference was found between the two groups in the amount of parenteral nutrition (286.2 ± 105 kcal vs. 477.5 ± 89.8 kcal; p = 0.204) or in maximum blood glucose level (233 ± 13 mg/dL vs. 222 ± 8 mg/d; p= 0. 711) within the first 48 hours. Unsurprisingly, after one month, significant improvement in serum albumin was found in the patients who received immediate enteral nutrition versus those who did not (2.26 ± 0.14 vs 1.82 ± 0.07; p = 0.0015).

Furthermore, in 2005, unpublished data from a poster presentation for the 34th Critical Care Congress, by Pellegrino et al. (Figure 1), reported that open abdomen patients are less likely to achieve adequate nutrition therapy during the first five post-operative days compared to closed patients post laparotomy. The cumulative caloric intake by five post-operative days was also found to be significantly lower in the open (OAP) as opposed to closed (CAP) group (3036 ± 1537 vs. 6089 ± 2245 kcal; p = 0.01), respectively. Similarly, a cumulative protein intake was (165 ± 99 vs. 334 ± 154; p = 0.03) in the same five-day period, while no significant difference was found between the two groups in average daily nitrogen balance (- 14.3 ± 4.7 vs. -11.4 ± 6.3; p = 0.38).

Figure 1 – Adapted from Poster Presentation: Gastrointestinal Disease or Dysfunction/Nutrition (Adult) II. Society of Critical Care Medicine 34th Critical Care Congress Phoenix, Arizona, USA, January 15-19, 2005. December 2004 - Volume 32 - Issue 12 - p A93.

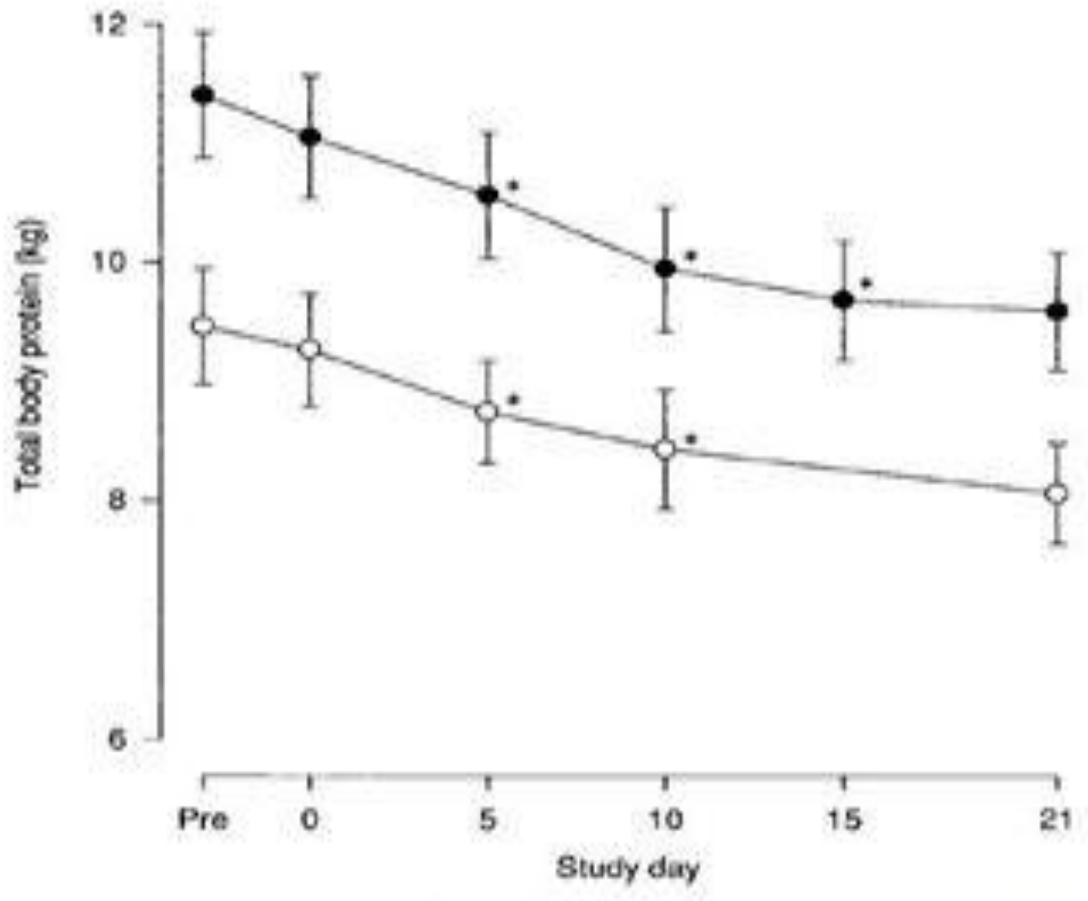
	Cumulative Caloric Intake (kcal)	Cumulative Protein Intake (gm)	% Estimated Caloric Goal	% Estimated Protein Goal	% Indirect Calorimetry Goal	Average Daily Net Nitrogen Balance
OAP	3036±1537	165±99	27±15	29±19	25±16	-14.3±4.7
CAP	6089±2245	334±154	52±22	57±28	41±25	-11.4±6.3
Significance	0.01	0.03	0.02	0.04	0.11	0.38

2.3.4 PROTEINS

The fundamental aim of nutrition therapy is to minimize protein catabolism and breakdown after the trauma insult. Optimum protein provision is an integral component of nutrition therapy that has been proven in several studies. However, an optimal amount of protein intake is a highly neglected area in the critical care population, as well as in patients managed with an open abdomen approach.[62-65] For example, in the critical care setting, most adults receive less than half of the most common current recommendation of 1.5 g protein /kg/day for the first week or longer of their stay in an intensive care unit.[63]

Moreover, Plank et al.[66] demonstrated changes in total body protein over a 21-day period. In both sepsis and trauma groups, losses were greatest during the first 10 days, ranging from 0.9% and 1.0% of total body protein per day during sepsis and trauma, respectively. Total protein lost over the study period averaged 1.21 ± 0.13 kg in the sepsis patients ($p < 0.0001$) and 1.47 ± 0.20 kg in the trauma patients ($p < 0.0001$). Approximately 70% of the total protein lost came from skeletal muscle, and this occurred in the first 10 and 5 days in the sepsis and trauma groups, respectively.

Figure 2 – Illustration for predicting total protein loss in 12 patients with severe sepsis (open circle) and 21 patients with major trauma (closed circles) over a 21-day period after onset of illness (Adapted from Plank et al.)(66)



Within the context of the open abdomen setting, the only study aimed at evaluating the effect of calculating abdominal fluid nitrogen as part of nitrogen balance estimations was conducted by Cheatham et al.[29] documented that open abdomen increases insensible protein loss, estimated as 2 gram of nitrogen per liter of abdominal fluid output, which should be taken into account during nutrition support. Furthermore, Powell et al.[31], Wang et al.[50], and Tsuei et al.[48] documented that an open abdomen approach may lead to significant fluid, electrolytes, and protein loss due to an exposed abdominal cavity.

2.4 RESTING ENERGY EXPENDITURE

2.4.1 OVERVIEW

Resting energy expenditure (REE) refers to the minimum number of calories needed to maintain basic life functions in a non-active state or rest. It is also known as resting metabolic rate (RMR).(67)Total Energy Expenditure (TEE) includes REE, thermic effect, and physical activity, where REE is approximately 60% to 70% of total energy expenditure, and thermic effect of food is approximately 8% to 10% of total energy expenditure; physical activity also refers to the growth and/or disease process, which includes the healing process. In the case of critically ill patients receiving ventilatory support, REE represents 75% to 100% of TEE, as long as a steady state is achieved to maintain cell membrane pumps, basic metabolic processes, and muscular function (Figure 3).(68-70)

The required resting energy expenditure can either be estimated with predictive equations or measured with indirect calorimetry. The gap between energy intake and the required REE remains a controversial issue. However, the energy target should be precisely determined and monitored to promote an anabolic state.(71)

2.4.2 METABOLIC RESPONSE TO TRAUMA

2.4.2.1 EBB AND FLOW PHASES

The hypermetabolic response to any catastrophic insult, such as the stress response that follows surgery, sepsis, trauma, thermal injury, and neurotrauma, is categorized into two phases: ebb and flow. During these phases, many hormonal and pathological changes occur. These changes are illustrated in detail in Figure 4.

The ebb (shock) phase lasts about 24 to 48 hours after insult, and is characterized by hypovolemic shock, hypotension, and tissue hypoxia. The primary therapeutic goal during this phase is fluid/blood resuscitation. The flow phase is comprised of two phases: the acute response and the adaptive response (Figure 5).

As metabolism is often escalated following injury, historical studies have shown that there are wide variations in both the magnitude and time course of metabolic rates, with energy expenditures ranging from 32% to 200% above those predicted for the non-injured state.[72] Furthermore, in stressed patients; the metabolic response of injury has been defined as the ebb and flow phases by several researchers.[69, 73] The injury itself can induce a series of dynamic metabolic responses with different characteristics in three stages: the ebb and flow phases, followed by a recovery or anabolic phase. Immediately after injury, the ebb phase begins and lasts between approximately 12 to 48 hours. This phase is characterized by hyperglycaemia, decrease in energy expenditure, a cardiac output, peripheral vasoconstriction, and increased sympathoadrenal activity. Then the flow phase starts at approximately 7 to 10 days post-injury, and continues as an anabolic phase over the next few weeks.

Energy expenditure changes during the acute phase of trauma, in a study by Roubenoff et al.,[74] cytokines were shown to increase energy expenditure to 9–10 kcal/d per ng/ mL. However, according to Cerra and colleagues,[71] cytokines increase daily energy needs by 10% to 20%.

Uehara et al.[68] showed that during the first week after the onset of major trauma or sepsis, resting energy expenditure increases up to a maximum of 40% above normal REE, which might be because of the potential theremogenic effect of nutrition support and the hyper-metabolic response of the trauma or sepsis. Researchers also reported that by the third week of illness, REE was still greater than normal by ≥ 20%.

In other study on severe head trauma, Raurich et al.[75] documented this type of trauma to be characterized by a state of hyper-metabolism in patients treated with and without morphine; in 25 of 80 (31%) patients, the values of measured REE were higher than the predicted REE by 130%. These results illustrated the impact of medications on REE.

Figure 3 – Three major components of daily energy expenditure

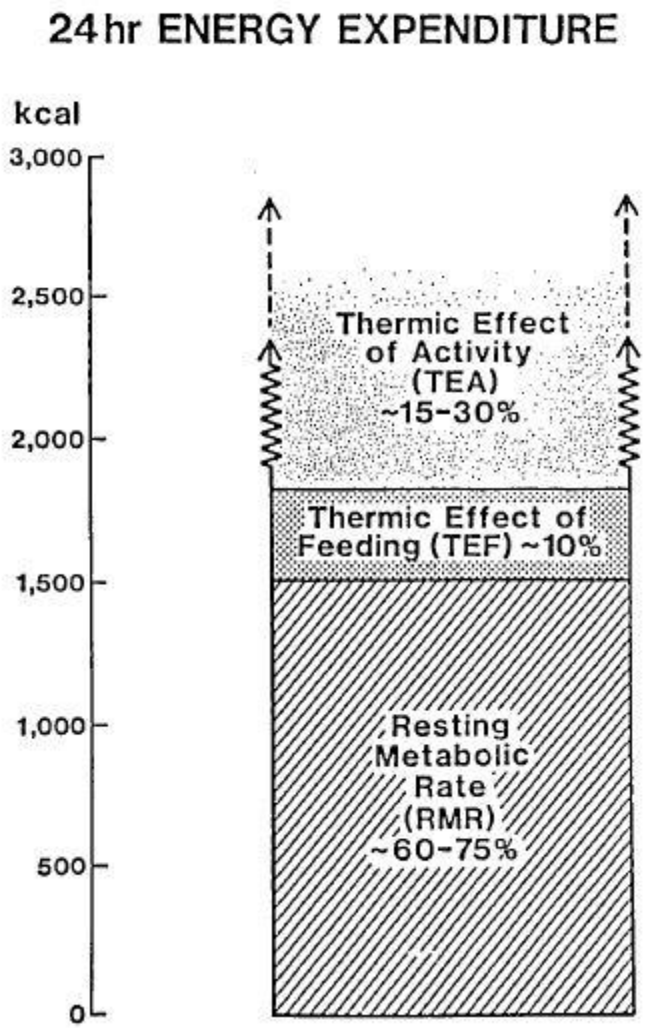


Figure 4 – Catabolic response to major insult occurs in phases

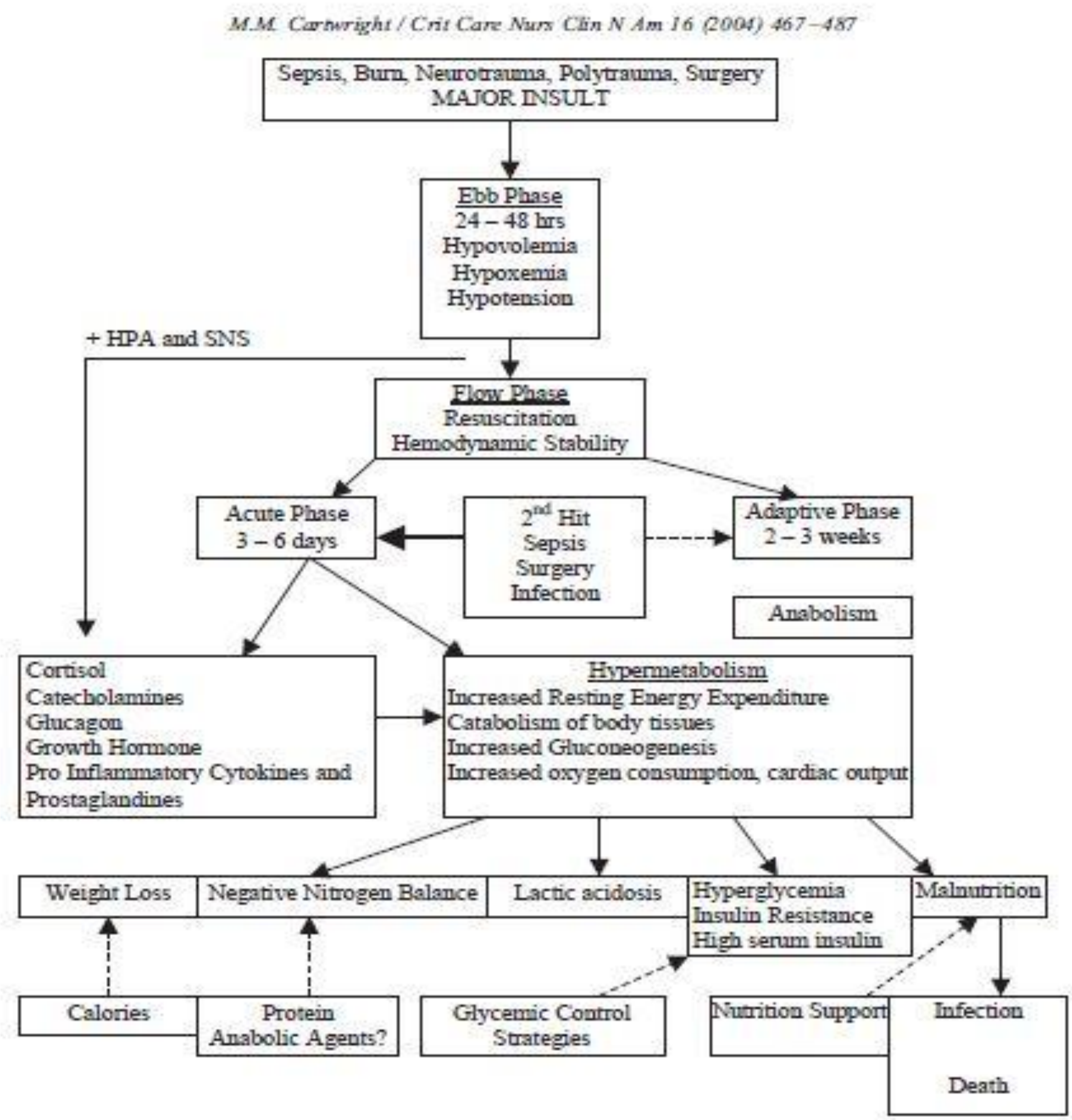
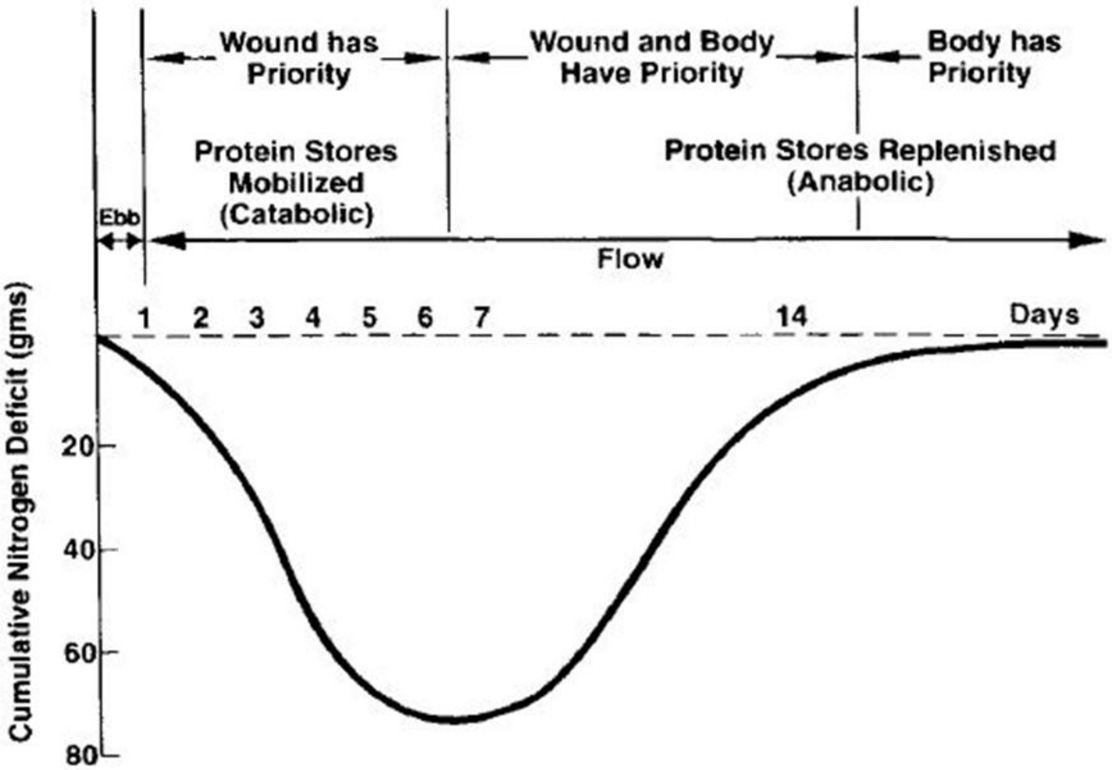


Figure 5 – Phases of metabolic responses of severe trauma



2.4.3 CONTRIBUTING FACTORS OF ESTIMATING REE

In dynamic predictive equations, despite the fact that body weight, height, temperature, and minute ventilation in addition to age and gender are the main independent contributors to estimates of REE,[76] there are other documented factors that may alter oxygen and carbon dioxide production and subsequently affect REE values. This includes, but is not limited to: stimulation of the sympathetic nervous system; changes to the mode of ventilation; administration of catecholamines, sedatives, anesthesia, temperature variations, and provision of nutrition during acute illness or surgical procedures. Therefore, metabolic variations represent a unique set of etiologies.[69, 77-83]

Despite the fact that some studies have produced varying factors contributing to measured REE, the literature offers incomplete and sometimes confusing evidence regarding different variations, as discussed below.

2.4.3.1 EFFECT OF TRAUMA OR INJURY

An early report conducted by Long et al.[72] studied the measured expenditures of various groups of patients categorized as burn, trauma, and sepsis. This report showed increases in REE compared to predicted REE. The data indicate that REE increases in all patients, and that there are trends of increases in REE dependent on the severity of the insult. Energy expenditure in the flow phase is elevated in proportion to the severity of the injury. It is highest following severe burns, when it rises by 60% to 70%. After elective abdominal surgery, it increases by about 5%, and with major injury and severe sepsis it increases by 30% to 40%. These increases are due to the general increase in metabolic activity, in particular the increased hepatic metabolism, and to an increase in the activity of various metabolic cycles, in particular the free fatty acid/triglyceride cycle (an energy consuming process), which is secondary to the increased sympathetic nervous activity.

2.4.3.2 EFFECTS OF TEMPERATURE AND SEDATION

Bruder et al.[81] studied the relationship between body temperature, sepsis, and energy expenditure in 24 head-injured sedated or non-sedated patients during the first 10 days after admission. This report stated that all of the differences in energy expenditure between various sedative regimens were due to variations in body temperatures. It is not clear whether the muscle relaxants or thiopental had an impact on energy expenditure, since some patients had been in more than one group previously sedated with fentanyl and midazolam. Moreover, a relationship between body temperature and energy expenditure was found in sedated patients, but was not found in non-sedated patients.

This study also reported that body temperature and sepsis are responsible for most changes in energy expenditure in sedated head injured patients. Fever increased energy expenditure by 10% per degree of Celsius, and sepsis increased energy expenditure independently of fever. Furthermore, the mean and maximum percentage increases in VO2 were 30% and 60%, respectively, after discontinuation of sedation with midazolam in severely head-injured patients.

Terao et al.[84] stated that increased depth of sedation induces a progressive decrease in VO2, and subsequently decreases REE in postoperative mechanically ventilated patients. Notably, in this study, there were no significant differences in mean arterial pressure, heart rate, or the dose of dopamine among the three states of sedation.

Sedation is the main contributor that affects REE. Osuka et al.[85] showed that neuromuscular blockade usage might be associated with the reduction of the metabolic rate of sedated ventilated patients with severe head injury under normothermia control by 13%, compared to predicted REE. Moreover, age, height, heart rate, and minute ventilation were significantly related to energy expenditure.

Furthermore, Bruder et al. reported that, during the first 12 hours after the discontinuation of sedation, severe head-injured patients experienced a large increase in VO2 and energy expenditure.[86]

As the predicted formula is based on body weight, height, minute ventilation, and body temperature, the measured resting energy expenditure is more relevant than the usual predictive equations for metabolically stable, mechanically ventilated patients.[3, 76]

2.4.3.3 EFFECT OF NUTRITION

During the early phase of injury, Jeevanandam et al.[73] studied the relationship between metabolic rate and infusion of glucose alone or infusion of TPN in severely injured trauma patients. In the fasting state, during the first 40 to 60 hours after injury, measured energy expenditure ranged from 28.8 to 35.9 kcal/kg, while it ranged from 31.3 to 36.0 kcal/kg after 4 to 6 days of injury in the feeding state.

Similarly, McCall et al.[87] examined the relationship between REE and nutritional status, reporting that the mean energy expenditure of patients in the fed state was 9% higher than patients in the fasted state (22.3 vs. 24.6 Kcals/kg, $p = 0.002$).

2.5 REE ESTIMATION

Various predictive formulae were obtained following the pioneering work of Harris and Benedict for the estimation of energy expenditure. However, in 2015, Tatucu-Babet et al.(88) reviewed discrepancies between 13 predictive equations'estimations and indirect calorimetry measurements in both individuals and groups. This study found differences ranging from 43% below and 66% above indirect calorimetry values. At the group level, of 13 predictive equations reviewed, 38% underestimated and 12% overestimated energy expenditure by more than 10% of indirect calorimetry measurements. The remaining 50% of equations estimated energy expenditure to within ± 10 of indirect calorimetry values. The Penn State equation is the most accurate among the other equations applied to critically ill patients, and is also what our institution are using in practice at our institution. Therefore, this review will discuss the Penn State equation in more detail.

2.5.1 PENN STATE EQUATION (1998, 2003)

In 2003, the Penn State equation was modified because of research that indicated that the Mifflin St. Jeor equation was more accurate than the Harris-Benedict equation in predicting resting energy expenditure; further, the use of adjusted body weight for obese patients in the Harris-Benedict equation tended to underestimate caloric need (Table 2). Penn State equations were found to be unbiased and valid by Frankenfield and colleagues, who found the 1998 Penn State equation to be 68% accurate, and the 2003 Penn State equation 72% accurate.

The 2003 Penn State equation successfully predicted resting energy expenditure in non-obese and obese elderly patients, and in non-obese young adults, but not in obese young adults.

Table 2 – The most common equations used to predict REE

Harris - Benedict	Men: 66.4730 + (13.7516 X weight kg) + (5.0033 X height cm) + (6.7550 X age)	
	Women: 655.0955 + (9.5634 X weight kg) + (1.8496 X height cm) + (4.6756 X age)	
Mifflin St. Jeor	Men : (10 X weight Kg) + (6.25 X height cm) – (5 X age) + 5	
	Women : (10 X weight kg) + (6.25 X height cm) – (5 X age) - 161	
1998 Penn State	(1.1 X Harris-Benedict*) + (140 X Tmax) + (32 X VE) - 5,340	
2003 Penn State(69)	(0.85 X Harris-Benedict**) + (175 X Tmax) + (33 X VE) - 6,433	
2003 modified Penn State(89)	(0.96 X Mifflin) + (167 X Tmax) + (31 X VE) - 6,212	
2003 modified Penn State(90)	(0.71 X Mifflin) + (85 X T-max) + (64 X VE) - 3085 (for elderly obese)	
* Adjusted body weight for obese patients		
** Actual body weight		
VE = Minute volume in L/min		
T.max = Maximum body temperature in the past 24 hrs. in Celsius		

2.5.1.1 ACCURACY AND VALIDATION OF PENN STATE EQUATION

As we are using the 2003 Penn State equation in our intensive care unit to estimate the nutritional needs of open abdomen patients, this thesis will focus on the validity of Penn State equations. Overall, the Penn State equation has been found to be the most accurate equation among other predictive equations that have been used in the intensive care unit when indirect calorimetry is not available.[88, 89, 91-93]

Several studies have documented the accuracy and the validity of Penn State equations. Accuracy refers to coming within 10% of the measured resting energy expenditure through the use of indirect calorimetry. In 2003, MacDonald and Hildebrandt[94] conducted a study using 76 mechanically ventilated medical-surgical patients to validate the Penn State equation in any patients who had a BMI < 30 kg/m. Their research showed that both the 1998 and 2003 Penn State equations had an overall accuracy of 29% and 39%, respectively.

Similarly, in 2004, Frankenfield et al.'s[89] validation study using 47 mechanically ventilated, medical, surgical, trauma patients showed that the 1998 and 2003 Penn State equations had an overall accuracy rate of 68% and 72%, respectively. Moreover, Frankenfield et al. categorized the patients based on weight, age, and age and weight combined. When the patients were categorized based on weight, the 1998 Penn State equation accuracy was 69%, or 67% for non-obese (n = 29) and obese (n = 18) patients, respectively. The 2003 Penn State equation accuracy was as high as 79% for non-obese patients (n = 29), but 61% for obese patients (n = 18). When subdivided the patients by age, where young age was defined as less than 65 years old and elderly as at least 65 years old, the 1998 Penn State equation accuracy was 63% for young individuals (n = 27) and 75% for elderly individuals (n = 20), while the 2003 Penn State equation's accuracy was 63%, or 85% for young individuals (n = 27) and elderly individuals (n = 20), respectively. Moreover, Frankenfield et al.[89] subdivided patients based on age and weight combined, finding that the accuracy of the 2003 Penn State equation was 67% for young, non-obese patients (n = 15) and 58% for young, obese patients (n = 12); the accuracy for elderly, non-obese patients (n = 14) and elderly, obese patients (n = 6) was 93% and 67%, respectively. In 2007, another study conducted by Boullata et al.[95] documented that among 141 ventilated patients in the intensive care unit, the overall accuracy of the 2003 Penn State equation was 43%.

A subsequent study by Frankenfield et al.[93] using 202 critically ill patients showed that the modified 2003 Penn State equation had the highest accuracy rates among the subgroups, except for the elderly obese group, which was not accurately predicted by any equation. For example, the accuracy of the modified Penn State equation was 77% for non-obese elderly patients, but only 53% accurate for obese elderly patients.

2.6 REE MEASUREMENTS

2.6.1 INDIRECT CALORIMETRY

Due to the prevalence of both underprescribed and overprescribed energy needs in critically ill patients, as determined by estimated equations, indirect calorimetry (I.C), also known as the metabolic cart, remains the most accurate method for determining energy expenditure in both inpatient and outpatient settings.[69, 88, 96-98]

The concept of indirect calorimetry involves determining the metabolic rate by measuring gas exchange, including whole body oxygen consumption (VO2), carbon dioxide release (VCO2), respiratory quotient (RQ= VCO2/VO2), and urinary nitrogen excretion. Indirect calorimetry calculates the energy expenditure for the patient by using the modified Weir equation: Weir equation: EE = (3.94 x VO2) + (1.1 x VCO2)

2.6.1.1 GENERAL RECOMMEDATION AND LIMITATIONS OF USING I.C

One of the most necessity conditions to obtain accurate measurements is to maintain a steady state. A steady state was defined as a period of five minute when the variation in vo2 and vco2 is less than 10%. It is also important to consider other aspects before the measurements such as prepare a quite atmosphere by avoiding nursing care and keeping the FiO2 constant during the measurements. The study should be delayed for approximately 1 hour after any change in ventilator settings or any painful procedure. It also has been recommended to wait 6-8 hours after general anesthesia and before starting the test.[99, 100]

Limitations of using the I.C can be due to either technical or logistic issues. Accurate assessment of REE and RQ may not be possible in situations preventing the complete collection of expired gases. For instance, air leaks from the ventilator circuit and around endotracheal tubes or through chest drains. High settings on conventional ventilation units, including a FiO2 above 60% or high-positive end-expiratory pressure (PEEP) levels, as well as the connection of the IC to ventilators with large bias flow may result in inaccurate measurements of REE. Owing to the limitations and considerations faced by REE measurements, indirect calorimetry has been underused for both healthy and ill individuals.

3. STATEMENT OF PURPOSE

3.1 RATIONALE

Understanding the importance of nutrition support, particularly in critically ill patients, is based on the known physiologic consequences of inadequate nutrition. The impacts of both underfeeding and overfeeding include, but are not limited to, reduced complications, faster recovery, and reductions in the overall cost of health care.[101]

The need to assess nutritional status and nutrition adequacy is becoming a critical aspect of patient management. Many researchers have studied the catabolic and hyper-metabolic states caused by trauma, burn, and injury. However, the evidence of nutritional status assessments on patients with an open abdomen is scant. Open abdomen patients typically experience a hyper-metabolic state with insensible loss of proteins and fluids. Therefore, it has become necessary to scale nutritional need with optimum targets to overcome the unparalleled feeding challenges that face open abdomen patients during the recovery phase in the intensive care unit.

Moreover, open abdomen patients are at high risk for inadequate nutrition therapy due to different causes, including:

1. Increased abdominal distention or bowel edema will consequently make obtaining definitive abdominal closure more difficult
2. Small bowel necrosis[60, 102] after jejunal tube feeding or stretching of low-perfused bowel
3. Ileus and feeding intolerance will lead to aspiration pneumonia
4. Infectious complications related to TPN use

Prior studies have also assessed the REE of trauma patients; however, these studies examined all surgical patients with and without traumas, and often did not separate out open abdomen patients in their analysis. Indeed, there are few reports addressing the metabolic status of trauma patients. With regard to open abdomen patients, there is not yet any study reporting the impact of the open abdomen technique on REE measurements. Thus, it remains unclear how the presence of an open abdomen might affect REE values and the metabolic state.

Furthermore, despite the fact that there has been a surge of research to improve current guidelines and provide a more suitable algorithm for feeding critically ill patients, the mechanically ventilated trauma patients represent a large group not rigorously studied in terms of energy expenditure measurements.

Taking all of this into consideration, it is important to determine the manner in which the open abdomen may lead to inadequate feeding until fascial closure. As a result of resuscitation, fluid overload and massive abdominal edema, delay closure of the abdomen promote a vicious cycle in open abdomen patients which could lead to unfavourable nutritional outcomes, such as a negative nitrogen balance as a result of the loss of fluid and protein from the peritoneal cavity.[2, 29, 31]

3.2 STUDY HYPOTHESES

This thesis hypothesizes that underfeeding is significant in the open abdomen population, and that achieving an optimum nutrition target will be associated with favourable outcomes. It is further hypothesized that open abdomen approach will require higher resting energy expenditure.

3.3 STUDY OBJECTIVES

Objectives are:

1. Describe and review current nutritional practices in patients with open abdomens in the intensive care unit
2. Compare energy intakes with Penn State equation targets to determine if open abdomen patients have been adequately fed
3. Compare resting energy expenditure (REE) measurements before and after closure of the abdomen to explore the impact of open abdomen on REE
4. Compare the measured REE through indirect calorimetry, with predicated REE values based on the Harris-Benedict equation

4. MANUSCRIPTS

4.1 MANUSCRIPT A (to be submitted)

Title:

FEEDING PRACTICES OF OPEN ABDOMEN PATIENTS: AN ASSESSMENT OF ENERGY INTAKE AND CLINICAL OUTCOMES

Authors:

Muhamad Elhusseini Hassan, Sameena Iqbal, Mostafa Alhaboubbi, Dan Deckelbaum, Lyne Stlaurent, Eleanor Eckert, Tarek Razek, Kosar Khwaja

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Meeting information: These results have been presented as a poster at the American Society for Parenteral and Enteral Nutrition (ASPEN) meeting on February, 16th 2015 at Long Beach, California,USA. [103]

Manuscript word count:

2,791

ABSTRACT

Purpose: The open abdomen (OA) procedure in the damage control setting has become more common. Optimizing nutritional support for OA patients continues to pose a challenge for surgeons. The objective of this study was to review current practices using the Penn State equation to determine if these critically ill patients were adequately fed.

Methods: A retrospective study was conducted on 33 patients admitted to the ICU with OA for minimum of 7 days at a Level 1 Trauma Centre between January 2010 and September 2013. Daily caloric and protein intakes were measured by tabulating the total enteral (EN) and/or parenteral nutrition (TPN) received, as well as the total relevant fluid and medication infusions. Patient demographics and standard outcome variables were recorded. The nutritional target using the Penn State equation was calculated for each patient. The mean percent target was calculated for the first week, second week, and for the first 14 days of ICU admission. The optimal energy needs were defined as ± 10 % of the target.

Results: The median age was 47 and 85% of patients were male. At 7 days, 6% of patients met 90% of mean target calorie and protein requirements. EN was successfully introduced in 21.2% of the patients, while 42.4% of the patients received TPN, 27.2% received combined nutrition, and 9% did not receive any form of nutrition support. At 8–14 days, 24% reached the caloric target with 55% achieving the protein target. Twenty percent received EN, while 43.3% received TPN and 40% received both TPN and EN. By the total 14 days of admission, 9% had achieved the mean protein and caloric targets. Unadjusted survival was higher in the group that met their target protein needs at 8–14 days, at 100% vs. 64% (P=0.011). TPN use was higher in the group who achieved the optimal protein intake target, at 68% vs. 13% (P=0.002).

Conclusion: The vast majority of OA patients were insufficiently fed during their ICU stay. Patients who achieved their protein target at 14 days had a higher survival rate. TPN use was also higher in the group who achieved the optimal protein target. However, achieving the optimum caloric target did not seem to affect clinical outcome. Further studies are needed to identify the impacts of underfeeding on OA patients.

INTRODUCTION

Implementation of damage control surgery and the open abdomen technique has showed improved survival in trauma and acute general surgery emergencies.[1] However, this technique has also created new challenges in the management of patients with a significant abdominal wall defect. One of the main challenges lies in optimizing resting energy expenditure (REE). Thus, under-feeding or over-feeding remains problematic due to uncertainties regarding the prediction of energy needs at different disease states as well as individual variations.[2] Early studies were conducted to explain the responses of injury and its influence on caloric and protein requirements. These studies showed that nutrition support after trauma should be dynamically adjusted according to metabolic responses. This is because the trauma itself can induce a series of dynamic metabolic responses with different characteristics in three stages: the ebb phase, flow phase, and recovery phase.[3, 4] The ebb phase typically lasts 12 to 48 hours, followed by the flow phase, which generally lasts 7 to 10 days, and finally the anabolic or recovery phase, which may extend to months.[5, 6] In the course of the flow phase, hyper-metabolism occurs as the body attempts to rehabilitate itself while maintaining organ functionality. This phase is characterized by insulin resistance and hyperglycemia, which increase pro-inflammatory cytokine production.[7] Cerra et al.'s study reported that cytokines increased daily energy needs by 10 to 20%.[8] Thus, even well-nourished patients may develop protein-energy malnutrition within 7 to 10 days of intensive care unit (ICU) admission.[9]

Estimate energy expenditure in critically ill patients by using predictive equations

Prediction equations are promptly available and universally used to estimate resting energy expenditures. In particular, the Penn State equation is widely used for critically ill, mechanically ventilated, and trauma patients to estimate the resting energy expenditure if the metabolic cart is not accessible.[10, 11] Both the 1998 and 2003 Penn State equations were found to be unbiased and valid by Frankenfield and colleagues, who found the 1998 Penn State equation to be 68% accurate, and the 2003 Penn State equation to be 72% accurate.[12]

Challenges associated with the open abdomen technique

Open abdomen patients often present with multiple injuries that require multiple surgeries, and they are also the most sick, critically ill, and subsequently the most hyper-metabolic of all surgical and trauma patients.[13] This hyper-metabolic state renders achieving caloric and protein targets extremely difficult. In addition, an open abdomen technique induces a significant source of protein and nitrogen loss in these critically ill patients, as confirmed by Cheatham et al.[14] Moreover, large amounts of protein loss across these wounds can result in changes in oncotic pressure at the capillary bed level. Protein loss can also induce the further loss of circulating volume into the interstitial space.[15] Furthermore, abdominal wall closure may not be possible either after major trauma or in septic patients for many reasons.[16, 17] Massive intestinal edema, risk of acute compartment syndrome, multiple re-explorations of the abdomen, as well as a triad of hypothermia, coagulopathy, and acidosis together may lead to prolongation of the hyper-metabolic state.[18, 6, 19] The purpose of this study was to compare our current practice with the Penn State equation target to determine if open abdomen patients were adequately fed.

MATERIALS AND METHODS

Study design

A retrospective review of all trauma and general surgery admissions from 1 January 2010 to 1 September 2013 was performed to identify patients who underwent exploratory laparotomy and subsequently required an open abdomen for seven days or more as a part of the damage control technique or after the development of acute compartment syndrome. These patients were subsequently transferred to the intensive care unit. Data for the review were obtained from hospital charts and from a prospectively collected ICU database.

Patient selection and data collection

The study includes a 14-day tracking period of all trauma and surgical patients who were admitted to the ICU and who had an open abdomen for seven days or more. For the purpose of the study, patients who had definitive fascial closure were no more considered an open abdomen patients. Demographic data included: age, sex, mechanism of injury, admission weight, body mass index (BMI), Injury Severity Score (ISS), Acute Physiology and Chronic Health Evaluation II (APACHE II), as well as initial albumin and pre-albumin, and hospital and ICU length of stay.

Nutritional assessment data and calculations

On patient admission, clinical nutritionist calculated energy expenditure based on the 2003 Penn State equation by using Mifflin St. Jeor equation. Penn state equation calculated as follows:

Energy Expenditure = 0.96 x (Mifflin St. Jeor) + 167 x (Maximum temperature) + 31 x (Minute ventilation) – 6212.

Where; Mifflin St. Jeor =Men: 10 ($weight_{kg}$) + 6.25($height_{cm}$) – 5(age) + 5

=Women: 10 ($weight_{kg}$) + 6.25($height_{cm}$) – 5(age) – 161

Total daily energy and protein needs derived from both enteral and parenteral nutrition formulae were calculated from each patient’s ICU flow sheets and the clinical dietitian’s orders.

Total enteral nutrition, such as Peptamen AF 1.2, Peptamen 1.5, Vivonex Plus, Isosource 1.5, and Promote, as well as TPN, any relative fluids such as dextrose and any medical infusion such as Propofol were calculated to determine the total kcal and protein in each cubic centimeter. Average nutritional intake was calculated and divided by prescribed nutritional target to get the mean percent target for three different timelines: first week, second week, and two weeks of ICU admission. Optimal energy needs were defined as ± 10 % of the mean target. The mean percent goal per ICU day was calculated as follows:[20]

$$\frac{\sum \frac{Each\ days\ energy\ intake}{Target\ energy\ intake}}{Number\ of\ ICU\ days}\ x\ 100$$

Independent variables such as route of feeding, technique of closure, duration of open abdomen, ventilation days, and any clinical outcomes such as sepsis, pneumonia, fistula, tracheostomy, wound infection, and intra-abdominal sepsis were also reviewed.

RESULTS

Patient characteristics

During the study period, the total open abdomen patients were 110. Thirty-five patients who had an open abdomen for seven days or more were enrolled in the study. Two of those patients were excluded due to incomplete data, leaving 33 patients for analysis (Table 1). The median patient age was 47 years. Eighty-five percent of the patients were males. Seventy percent of the patients were trauma patients, while 30% were general surgery patients. Blunt mechanisms of injury were more common than penetrating trauma (60% vs. 40%). Thirty percent of the patients were obese, with a BMI ≥ 30. Among the 33 patients with open abdomens, the mean prescribed caloric and protein target was 1982.7 ± 422 Kcal/day and 112 ± 27 gram/day, respectively.

Route of feeding and nutritional targets

The patients' mean percent goals were calculated and compared at three different points in time: first week, second week, and two weeks of ICU admission (Figures 3 and 4). Route of feeding was also evaluated at the same timeline. During all the timeline points, average energy and protein intakes were significantly lower compared to prescribed nutritional targets with a statistically significant difference ($p = <0.0001$) (Figures 1 and 2).

In the first week, the average daily calorie and protein intakes delivered were 997.3 ± 380 Kcal/day and 44.6 ± 27.5 gram/day, respectively. Enteral nutrition (EN) was successfully introduced in 21.2% of the patients, while 42.4% received total parenteral nutrition (TPN), 27.2% received combined nutrition (EN+TPN), and 9% did not receive any form of nutrition support. Six percent of patients met more than 90% of their target calories and protein. During the second week, the average daily calorie and protein intakes delivered were 1451.1 ± 680 Kcal/day and 81.6 ± 43.9 gram/day, respectively. Twenty percent of patients received EN, while 43.3% received TPN, and 40% received both TPN and EN. Fifty-five percent of the patients achieved ≥ 90% of their protein intake target, while 24% achieved the optimal caloric target.

Over two weeks of ICU admission, an average delivered calorie was found to be significantly lower as opposed to prescribed caloric target (1224.2 ± 439 kcal/day vs. 1982.7 ± 422.8 kcal/day; $P < 0.0001$). Similarly, an average delivered protein was significantly lower compared with prescribed protein target (63.2 ± 30.5 g/d vs. 112 ± 27 g/d; $p < 0.0001$).

Thirty-three percent of patients received TPN. Only 15.1% received EN and 51.5% received combined TPN and EN nutritional support. Nine percent of the patients achieved the optimal caloric and protein targets.

Clinical outcomes

In the second week, patients were divided into two groups on the basis of the optimal and suboptimal protein targets (Table 2A). Univarate analysis showed no significant difference in patients' baseline characteristics, such as age, gender, BMI, Injury Severity Score (ISS), APACHE II score, as well as prescribed caloric and protein targets, was identified. As expected, the group who met ≥ 90 % of the protein target, had a significant higher average delivered protein than the suboptimal group (115.8 ± 17.5 vs. 49.4 ± 35.9 gram/day, P = <0.0001). There was no statistically significant difference between both groups in clinical outcomes such as sepsis, pneumonia episodes, duration of open abdomen, and length of ICU stay. However, the unadjusted survival rate was significantly higher in the group who met ≥ 90 % of the protein target (100% vs. 64%, P = 0.011). Also, the proportion of TPN use in the group who achieved the optimal protein target was significant compared to the suboptimal group (68% vs. 13%, P = 0.002) (Table 2B). The average initial day of TPN use was earlier in those who met ≥ 90% of the protein target compared to the suboptimal group (3 ± 1 vs. 6 ± 3.5 days, P = 0.017).

During the same period, a univariate analysis was performed between the optimal and suboptimal caloric target (Table 3A). Between day 8-14, the patients who met ≥ 90% of the caloric target received, on average, 1994.7 ± 436 Kcal/day, while those who met < 90% of the prescribed target received, on average, 1304.8 ± 665 kcal/day (P = 0.021). Furthermore, there was no statistically significant difference between both groups in baseline characteristics data, such as age, gender, ISS, APACHE II score, prescribed caloric and protein targets, as well as the route of feeding or any standard clinical outcomes such as survival, pneumonia episodes, sepsis, the length of ICU stay, or the duration of open abdomen (Table 3B).

DISCUSSION

The fundamental goal of nutritional support is to meet energy and protein needs and to minimize protein catabolism. This study investigated the adequacy of nutritional support over 14 ICU days in 33 patients who had an open abdomen for seven days or more after trauma or general surgery emergencies. We observed that critically ill patients were insufficiently fed during their two-week stay at the ICU according to traditional nutritional targets. In previous studies, malnutrition seemed to be a considerable problem in the surgical ICU.[21, 22] Similarly in Canadian ICUs, Heyland et al. reported that 16% of patients who stayed more than three days in the ICU did not receive any nutritional support. Furthermore, during their first 12 days in the ICU, the patients who received nutritional support achieved only 56% to 62% of their estimated energy needs.[22]

Nutritional intake and Outcomes

To the best of our knowledge, this is the first study performed that explore the sufficiency of the nutrition offered to open abdomen patients with delayed fascial closure. The primary aim of the study was to determine if open abdomen patients were adequately fed. The data elaborated that an average delivered calories and protein was significantly lower compared to prescribed target during different timelines. Given that the delivered energy and protein were collected from various sources such as TPN, dextrose infusion as well as medications such as propofol. Our results also demonstrated that 6% (2/33) of the patients achieved 90% or more of the mean calories and protein target by day 7. The optimal caloric and protein target, however, has been achieved in 24% and 55% during the second week, respectively. This finding is consistence with other study conducted by Hise et al.[20] who concluded that minority of medical and surgical ICU patients reached 70% of dietitian recommendation. In contrast, Tsuei et al.[23] reported that 57% (8/14) of open abdomen patients who received EN with duration ranging between 4 to 35 conservative days met at least 80% of estimated or measured energy expenditure. Because open abdomen patients with delayed abdominal closure had multiple injuries that require multiple surgeries, interruption of feeding could be the main reason of inadequate feeding. Other study reported that surgery (27%) is the most common cause of feeding interruption in trauma ICU patients. [24] Checking gastric residual volume and feeding intolerance's causes in such patients' population remain to be studied. Closer assessing of nutrition tolerance including proteins will ultimately provide a rationale for underfeeding open abdomen patients.

Failure to meet the prescribed target has been shown to prompt adverse outcomes.[25-28] It is interesting to note that unadjusted survival rate was significantly higher in the group who achieved ≥ 90% of protein target and the rate of TPN use was also higher in the same group. The present study suggests that patients with delayed closure of the abdomen may need TPN and adequate nutritional supply. In patients without open abdomen, similar finding was observed by Woodcock et al.[29] who found high mortality rate and high incidence of inadequate nutrition in the group received EN. In cancer patients, Pearlstone et al.[30] documented that level of plasma amino acid repletion was much higher in patients who had received TPN compared to EN or Libitum oral feeding. The study's findings will be confounded by possibility that non-open abdomen patients or patients with early closure of abdomen are healthy and more likely to tolerate the nutrition and thereafter enhance the benefit of nutrition supply.

On the other hand, our data showed that achieving optimal caloric target seems not to affect the survival rate. In agreement with Strack van Schijindel[26] who found that achieving both energy and protein target in mechanically ventilated critically ill patients had significant better survival rate than those achieve only energy target. Similarly, a randomized control trial conducted by Arabi et al.[31] concluded that permissive underfeeding (40 – 60% of caloric requirements) while reaching the protein target had no significant mortality rate compared to the group achieved standard full caloric target.

Other clinical outcomes such as sepsis, pneumonia, ICU length of stay, and duration of open abdomen was not significant between optimal and suboptimal protein or caloric intake. Our data also reflected that provision optimal amount of energy and early feeding might not be important in determining outcomes. Moreover, early feeding (≤ 4 days) may not in fact be a crucial factor to achieve optimal amount of calorie and protein. Previous studies have reported improved outcomes with early EN in trauma patients with or without open abdomen[32, 33, 34] For instance, in open abdomen study conducted by Dissanaike et al[32] showed early enteral feeding has significantly less rate of pneumonia compared with control group (43.8% vs 72.1%, p = 0.008). However, no significant difference in mortality, length of ventilator days, ICU days or hospital days was observed between groups.

The present study is different from other studies because of many reasons. Firstly, the study investigated the adequacy of both calorie and protein in open abdomen patients, in particularly, with a delayed abdominal closure. The study further investigated the impact of achieving the optimal target on clinical outcome. Secondly, the delivered energy was collected from various sources, namely, TPN, dextrose infusion and Propofol.

Our study has substantial limitations; this is a retrospective study with a small sample size and with no distinction made between trauma and general surgery patients. Lack of biomedical nutritional markers at the time of admission may also add to its limitations because it is hard to determine whether the patients were underfed or adequately fed at the time of surgery. Assessing daily urinary nitrogen balance and non-urinary nitrogen losses from diarrhea, fistula and abdominal fluid will provide a complete picture of adequate protein intake. We believe that these findings should be confirmed by large prospective and multi-center studies.

CONCLUSIONS

Based on the Penn State equation estimation, the vast majority of open abdomen patients in this study were insufficiently fed during their two weeks of ICU stay. Patients who achieved their protein target at 14 days were more likely to survive than the group who did not achieve that target. As well, TPN use was higher in the group with a higher survival rate. Achievement of optimum calories, however, did not seem to affect patient clinical outcomes. Due to many challenges associated with open abdomen patients, the careful monitoring of their energy needs may potentially improve their nutritional status and subsequently their clinical outcomes. Further studies are needed to investigate the correlation between outcomes, initiation of feeding, and the route of feeding in this critically ill population.

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Table 1 – Patients' baseline and clinical characteristics

Patients' characteristics		(n = 33)
Variables		Mean ± SD (Median)
Number of patients		33
Age	years	46 ± 19 (47)
BMI	n	25 ± 4.4(25)
Gender ratio	Male/Female%	85/15
Length of ICU stay	days	32.6 ±20 (26)
Length of hospital stay	days	79 ± 58.8 (64)
Prescribed daily caloric target*	Kcal/day	1982.7 ± 422 (2000)
Average daily calories delivered	Kcal/day	1224.2 ± 439
Prescribed daily protein target	gram/day	112 ± 27 (114)
Average daily protein delivered	gram/day	63.2 ± 30.5
Day of start EN (n=21)	days	5.43 ± 3.1
Day of start TPN (n=28)	days	4.24 ± 2.8
APACHE II Score	n	28 ± 8.8 (27)
Injury Severity Score (ISS)	n	27 ± 14 (25)
Obesity (BMI ≥ 30)	%	30
Type of trauma	Blunt/Penetrating %	60/40
Type of patient	Trauma/General surgery %	70/30
14 days morality	% (n)	12 (4)
In-hospital mortality	% (n)	18 (6)
*(Penn State equation)		

Table 2A – Univariate analysis of patients' characteristic between optimal and suboptimal proteins intake in week 2 (days 8–14)

Variables	Met $\geq$ 90% of proteins target (N=16)	Met < 90% of proteins target (N=17)	Sig. P Value
Gender (Male/Female)	(14/2)	(14/3)	P = 0.530
Age (IQR)	35.5 (28-52.25)	55 (32.50-68)	P = 0.094
BMI	26.2 ± 3.5	24.7 ± 5.1	P = 0.377
APACHE II	26.5 (19.25-30.25)	29.5 (23-34)	P = 0.270
Injury Severity Score (ISS)	20 (17-37)	29 (18.50-37)	P = 0.277
Penn state equation target (kcal/day)	2127 ± 341	1847 ± 456	P = 0.074
Prescribed protein target (gram/day)	111.25 ± 17.53	112.65 ± 34.32	P = 0.790
Average protein delivered in 2nd week	115.81 ± 17.5	49.41 ± 35.9	P = <0.0001*
Average protein delivered in 14 days	87.88 ± 17	39.88 ± 20	P = <0.0001*
Day of start TPN	3 ± 1.2 (16/16)	6 ± 3.5 (12/17)	P = 0.017*
Day of start EN	6.5 ± 4.6 (6/16)	5 ± 2.2 (15/17)	P = 0.622
Early feeding $\leq$ 4 days	81.2% (13/16)	70.6% (12/17)	P = 0.381
TPN	68% (11/16)	13% (2/15)	P = 0.002*
EN	0% (0/16)	40% (6/15)	P = 0.007*
Combined feeding	31.2% (5/16)	46.7% (7/15)	P = 0.305
TPN use in 14 days	56.2% (9/16)	11.8% (2/17)	P = 0.009*

Table 2B – Univariate analysis of clinical outcomes between optimal and suboptimal proteins intake in week 2 (days 8–14)

Variables	Met ≥ 90% of proteins target (N=16)	Met < 90% of proteins target (N=17)	Sig. P value
Duration of open abdomen (days)	24 (11.75-50.75)	14 (8.50-37)	P = 0.245
Length of ICU stay	27.5 (21-39)	24 (15-48)	P = 0.631
Sepsis	37% (6/16)	47% (8/17)	P = 0.420
Pneumonia	37% (6/16)	35% (6/17)	P = 0.642
Survival	100% (16/16)	64% (11/17)	P = 0.011*

Table 3A – Univariate analysis of patients' characteristics between optimal and suboptimal caloric intake in week 2 (days 8–14)

Variables	Met ≥ 90% of caloric target (N=7)	Met < 90% of caloric target (N=26)	Sig. P value
Gender (Male/Female)	6/1	22/4	P = 0.718
Age (IQR)	38 (28-53)	49.5 (28-65.5)	P = 0.308
BMI	24.8 ± 4.3	25.5 ± 4.5	P = 0.706
APACHE II	32.2 ± 11.8	27 ± 7.7	P = 0.281
Injury Severity Score (ISS)	31.8 ± 23.3 23 (16.25-56)	27 ± 12.7 25 (17.25-32.5)	P = 1.000
Penn State equation target (Kcal/day)	1935.7 ± 392	1995.4 ± 437	P = 0.682
Prescribed protein target (gram/day)	103 ± 21.1	114.4 ± 28.3	P = 0.352
Average calories delivered in 2nd week	1994.7 ± 436	1304.8 ± 665	P = 0.021*
Average protein delivered in 2nd week	113.7 ± 22.7	73 ± 44.4	P = 0.027*
Average calories delivered in 14 days	1590 ± 318	1126 ± 418	P = 0.008*
Day of start TPN	2.7 ± 1.4	4.8 ± 3	P = 0.090
Day of start EN	7.5 ± 3.5	5.2 ± 3	P = 0.286
Early feeding ≤ 4 days	85.7% (6/7)	73.1% (19/26)	P = 0.444
TPN	71.4% (5/7)	33.3% (8/24)	P = 0.087
EN	0% (0/7)	25% (6/24)	P = 0.183

Table 3B – Univariate analysis of clinical outcomes between optimal and suboptimal caloric intake in week 2 (days 8–14)

Variables	Met ≥ 90% of caloric target (N=7)	Met < 90% of caloric target (N=26)	Sig. P value
Duration of open abdomen (days)	26 (17-56)	17 (9.75-36.5)	P = 0.352
Length of ICU stay (IQR)	37.7 ± 32.3 24 (21-31)	46.7 ± 98.4 26 (17.75-43)	P = 0.747
Sepsis	28.6% (2/7)	46.2% (12/26)	P = 0.348
Pneumonia	57.1% (4/7)	30.8% (8/26)	P = 0.198
Survival	100% (7/7)	76.9% (20/26)	P = 0.208

Figure 1 – Mean difference between prescribed and delivered calorie.

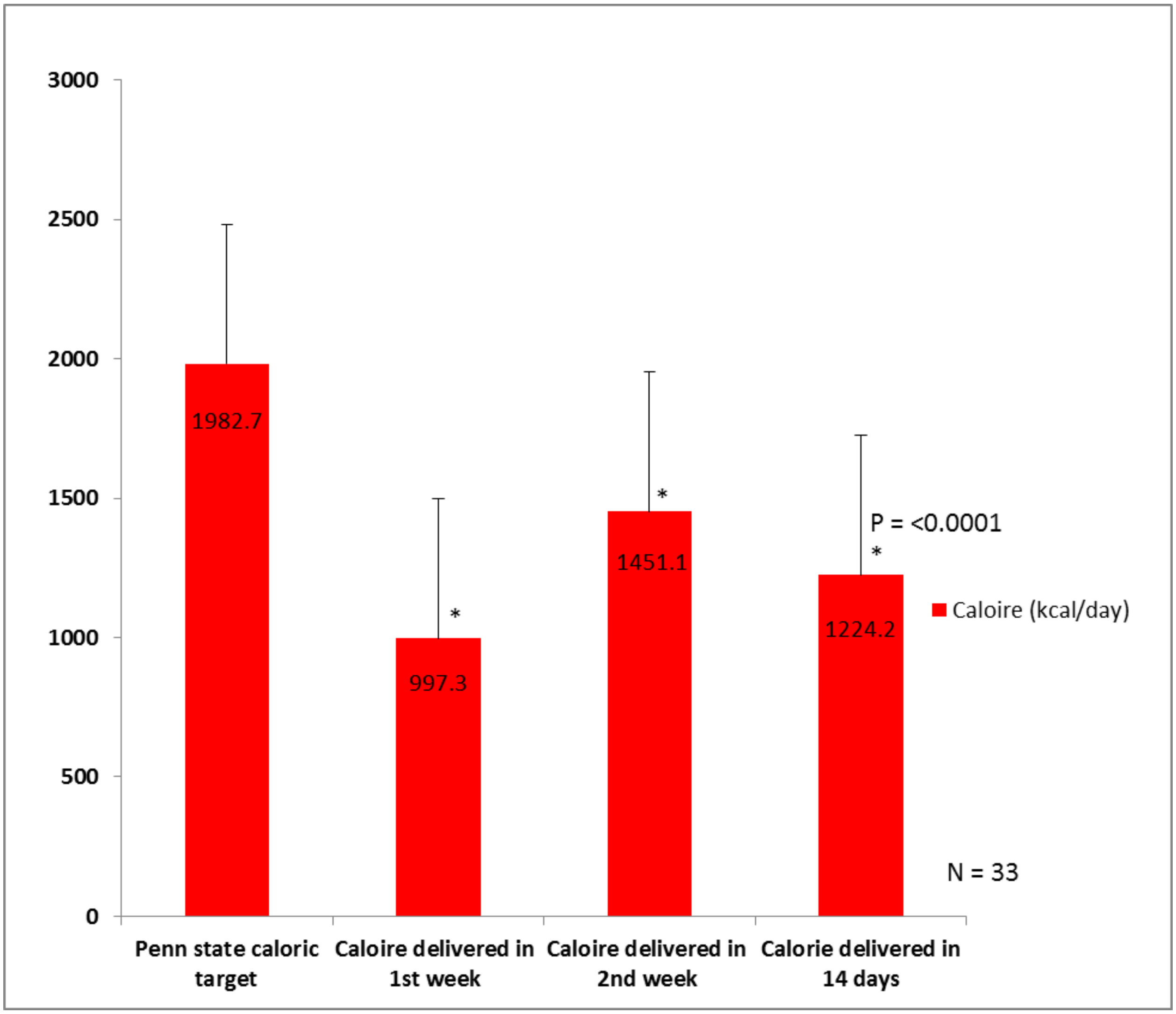


Figure 2 – Mean difference between prescribed and delivered protein

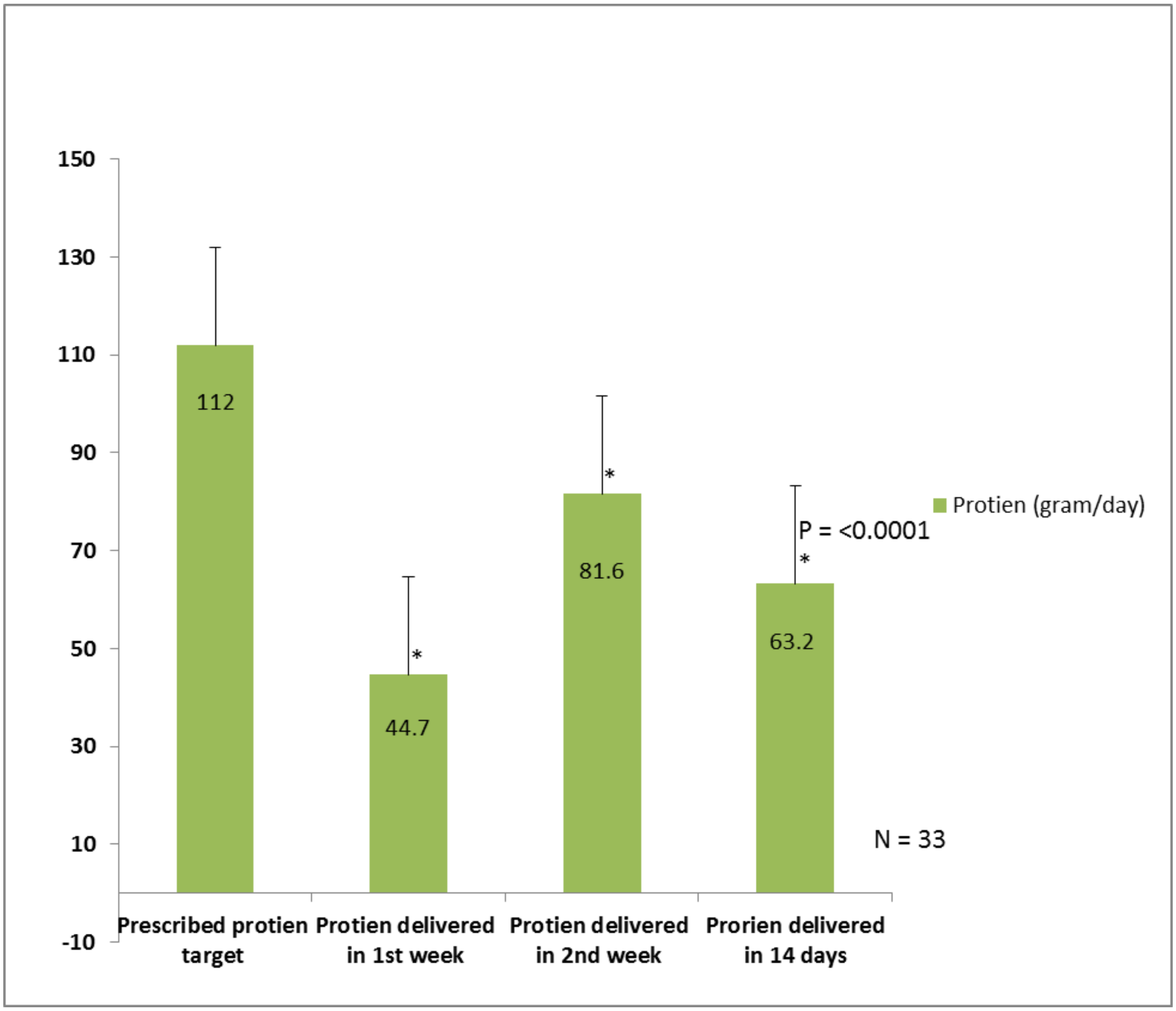


Figure 3– Percentage of open abdomen patients achieving optimal nutritional needs

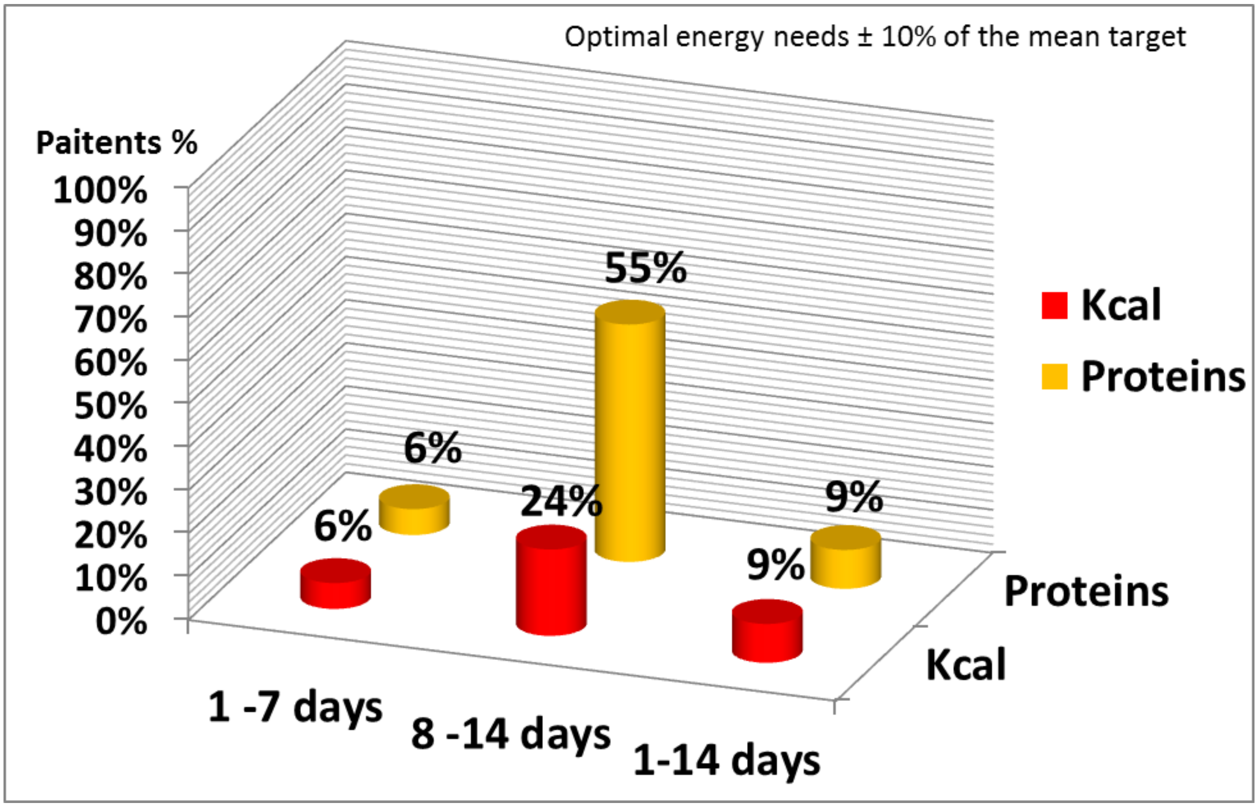
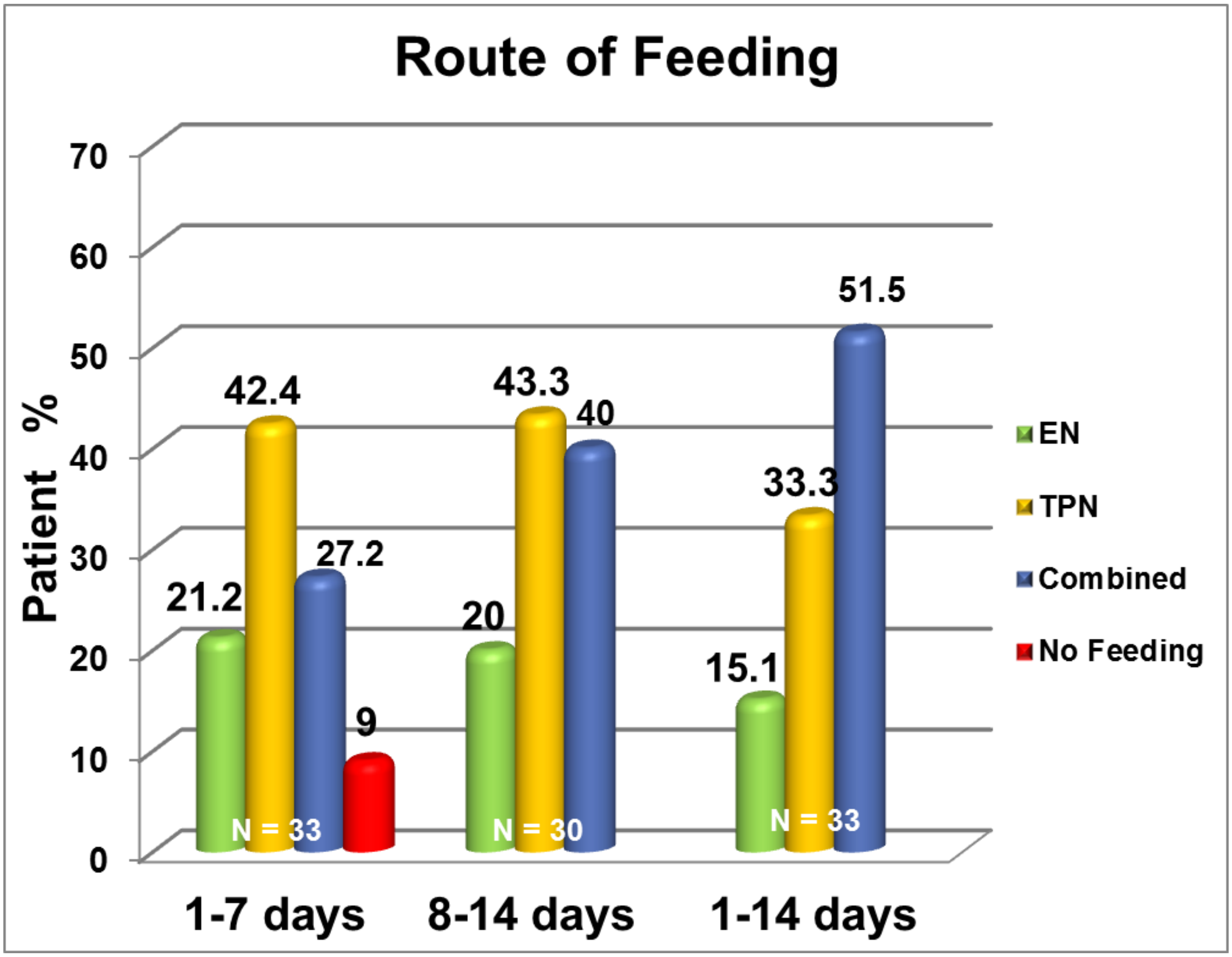


Figure 4 – Route of feeding over two weeks of ICU admission



4.2 MANUSCRIPT B (to be submitted)

Title:

MEASURED RESTING ENERGY EXPENDITURE IN PATIENTS WITH AN OPEN ABDOMEN: DATA OF PROSPECTIVE PILOT STUDY

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ABSTRACT

Background: Resting Energy Expenditure (REE) can be affected by various factors in acute illness. However, the relationship between an open abdomen (OA) and the measured REE remains unclear. Our objective is to explore the impact of OA on REE and determine other potential factors that may influence REE in OA patients.

Method: A prospective study was conducted on seven mechanically-ventilated non-septic OA patients admitted to the ICU at a Level 1 Trauma Centre between August and December 2014. Indirect calorimetry was used to measure REE before and after abdominal closure. Body temperature, sedation medications, and route of feeding were evaluated at the time of each measurement. Patients' demographic, predicative equations and standard clinical outcomes were recorded.

Results: A total of 31 REE measurements were performed (16 before vs. 15 after closure) in seven OA patients. The before abdominal closure measurements of REE were lower compared to after closure (1770 vs. 2179kcal/day, respectively, $P=0.012$). Furthermore, before abdominal closure, Propofol, Fentanyl, and Levophed use was significantly higher than after closure ($P=0.033$, $P=<0.0001$, $P = 0.043$, respectively). However, body temperature, proportion of enteral feeding, and pneumonia were higher after abdominal closure ($P = 0.027$, $P = 0.053$, $P = 0.043$, respectively). There is a significant unadjusted correlation between REE and temperature ($P=0.001$, $r2=0.29$). No significant correlation was identified between REE and abdominal status in the multivariate generalized estimating equation using repeated measures.

Conclusion: This pilot study identifies several factors that are associated with an increased measured REE after abdominal closure. Careful monitoring of REE may better guide nutritional targets in open abdomen patients.

INTRODUCTION

Injuries continue to have a significant growing health burden on population's worldwide.[1] Currently, the open abdomen (OA) procedure in the damage control setting has gained a broad interest among trauma and acute care surgeons. It is becoming apparent that a multifaceted approach is necessary to generate significant improvements in clinical outcome before and after closure of the abdomen following an exploratory laparotomy.

Owing to the effects of stress and the injury, resting energy expenditure (REE) is often fluctuating, inconsistent, and unpredictable; it is therefore becoming essential to identify energy requirements more precisely.[2] In the same context, the need for understanding each factor that affects REE is integral to successfully determining nutritional needs.

Currently, all explored methods to estimate REE have substantial limitations in terms of effectively determining nutrition targets compared with indirect calorimetry (IC), which provides the most accurate targets in a broad range of patients with altered metabolic states, different body sizes, and age extremes.[3] Therefore, all efforts explored have substantial challenges when it comes to effectively assessing optimum nutrition requirements in the acute care setting.

In clinical nutrition guidelines, the measurement of resting energy expenditure through the use of indirect calorimetry has been recommended as an important component of comprehensive nutritional assessment. However, due to several technical or logistic obstacles to using IC, many mathematical equations are still widely used to determine the energy requirements of critical ill patients. For the most part, predictive equations have been established and validated for both outpatient and inpatient settings, but not specifically for the Intensive Care Unit (ICU) setting.

Prior studies attempted to identify factors that may influence REE's value. The open abdomen itself in trauma and acute care surgery patients following laparotomy could attribute to derangements in REE values, along with other factors, such as change of clinical status, BMI, body temperature, altered levels of sedation, as well as use of other medications.

The main objective of the current study was to assess energy requirements in mechanically ventilated patients with an open abdomen to determine factors that could potentially influence metabolic response. In this prospective study, we investigated the impact of open abdomen on the metabolic rate of mechanically ventilated, non-septic, open abdomen patients during the early phase of trauma.

METHODS AND MATERIALS

Study design

A prospective study of all trauma admissions was performed between August and December 2014 to identify patients who underwent exploratory laparotomy and subsequently required an open abdomen as part of the damage control techniques implemented.

Patients were enrolled in the study if they were intubated, hemodynamically stable, and had an open abdomen for at least one day. Patients were excluded from the study if they were not on mechanical ventilation and not intubated, if there was any medical or surgical instability, or if the patient was known for any complications that could interfere with metabolic requirements such as sepsis, cancer or any chronic infectious disease such as HIV.

The measurements were performed once at least six to eight hours had passed after general anesthesia. The measurements were also delayed for one hour after any painful procedures.

Resting energy expenditure's measurements were performed through the use of indirect calorimetry during the first week pre and post closure of the abdomen. These measurements were delayed if a steady state was not maintained, or if the fraction of inspired oxygen (FiO2) was > 60%, the positive end-expiratory pressure (PEEP) was > 12 mm Hg, agitation existed, or there was any leakage from the chest tube.

Extubation was the primary end point of the study. The second end point was when the abdomen was closed and the patient was discharged prior to one week of admission.

Patient demographics data and entry criteria

Data was obtained from manual ICU flow sheets, computerized charts, and the hospital database for all trauma patients who were admitted to the ICU and had an open abdomen. On admission, demographic data, including age, sex, weight, height, mechanism of injury, body mass index (BMI), Injury Severity Score (ISS), Acute Physiology and Chronic Health Evaluation II (APACHE II), and hospital and ICU stay, were all reported from the ICU from day one. Clinical nutrition targets based on the Penn State equation were also reviewed.

The variables encompassed route of feeding, body temperature, duration of open abdomen, level of sedation, sedative medications, number of chest tubes, and any clinical outcomes such as sepsis, pneumonia, fistula, tracheostomy, wound infection, and intra-abdominal sepsis were also reviewed.

Protocol and measurement of energy expenditure

Indirect Calorimetry measurements

After warming up the indirect calorimetry for 10 minutes and achieving a steady state, each measurement took 15 to 25 minutes. The values of FiO2, PEEP, PO2 were reviewed and the clinical stability of the patient was ensured; each measurement was conducted with strict adherence to steady state for accurate results. During the course of the measurements, the difference between inspired and expired tidal volume was evaluated to make sure that there was no leakage from the endotracheal tube, which may lead to inadequate ventilation and improper readings. Most measurements were undertaken early in the morning (between 06:00 and 07:00) or late in the evening (between 22:00 and 24:00) to minimize errors related to unsteady state.

RESULTS

During a 16-week period, of the 10 patients who required open peritoneal cavity management, 7 patients were enrolled in the study prior to abdominal closure. Three open abdomen patients were excluded from the study. The first patient was hemodynamically unstable and died within 48 hours. The second patient excluded was known to have a chronic HIV infection; the third was a surgical patient with an esophageal cancer.

The mean age of the patients was 63 years, and 5 days was the mean duration of open abdomen (Table 1).Thirty-six measurements were carried out before and after closure of the abdomen (Figure 1). Each measurement took between 15 and 25 minutes; five measurements were excluded due to fluctuation and respiratory instability, leaving 31 measurements for analysis. Most of the measurements were carried out in the first three days, both pre and post closure of the abdomen.

Pre and post closure measurements

A total of 31 REE measurements were performed: 16 before and 15 after closure of the abdomen (Figures 2 and 3). Univarinate analyses between REE measurements before and after abdominal closure were performed, and showed that REE measurements before closure of the abdomen were significantly lower compared to after closure (1770 vs. 2179 kcal/day, respectively, P=0.012). Moreover, the mean predicted REE (Penn state) before closure of the abdomen was 1900 ± 390 kcal/day while measured REE was 1770 ± 415 kcal/day. When the abdomen was closed the mean predicated REE (Penn state) was 1930 ± 329 kcal/day while the measured REE was 2179 ± 381 kca/day. The hypermetabolic state were also observed between predicated basal metabolic rate (BMR) by using Harris-Benedict equation and measured REE before and after closure of the abdomen (109% BMR vs 128% BMR, respectively).

Furthermore, before closure of the abdomen, Propofol, Fentanyl, and Levophed use were significantly higher than after closure (P = 0.033, P = 0.0001, P= 0 .043, respectively). However, the proportions of enteral feeding as well as pneumonia episodes were higher after closure of the abdomen (P = 0.053, P = 0.043).

Despite the Richmond Agitation Sedation Scale [RASS] showing no significant difference between REE pre and post closure of the abdomen, REE values were significantly lower in the Fentanyl group compared to the non-Fentanyl group (2230 ± 298 vs 1842 ± 416; P = 0.035) (Figures 4, 5, and 6). Similarly, the mean REE values were significantly lower in the Levophed group compared to the non-Levophed group (1759 ± 432 vs 2099 ± 408; P = 0.048). However, Propofol had no effect on mean REE values (1904 ± 447 vs 2231 ± 342; P = 0.0117).

On the other hand, REE values were significantly higher in the feeding (EN + PO) group compared to the non-feeding (NPO) group (2135 ± 344 vs 1815 ± 471 p = 0.031) (Figures 7 and

8). Pneumonia had no effect on REE values (2191 ± 436 vs 1934 ± 443, p = 0.262).

In terms of a relationship between measured REE and abdominal status, no significant correlation was identified in the multivariate analysis (Figure 9). While controlling for abdominal status and sedation medications, the only significant parameters that affected REE was the body temperature; a weak significant unadjusted linear correlation was found between REE and temperature (P=0.001, R^2=0.29).

According to supermen correlation, prior to closure, the measured REE correlates well with Penn State (p = 0.0005 with correlation coefficients 0.9643) and there is a trend towards correlation between measured REE and HB (p = 0.0713 with correlation coefficient of 0.7143). After closure, the measured REE correlates well with Penn State (<0.0001 with correlation coefficients 1.0) and there is no correlation of measured REE with HB (p = 0.5046 with correlation coefficients of 0.4).

According to Bland - Altman analysis, the mean bias between measured REE and Harris Benedict (HB) equation before and after closure of the abdomen were (323.33 ± 429.49 kcal/day, 537.45 ± 399.52 kcal/day, respectively). While, the mean bias between measured REE and Penn State equation before and after closure of the abdomen were (39.48 ± 302.08 Kcal/day, 178.65 ± 165.45 kcal/day, respectively). (Table 3)

DISCUSSION

This pilot study aimed to assess the energy requirements pre and post closure of the abdomen. An unexpected dynamic increase in measured REE was identified after closure of the abdomen compared to before closure of the abdomen. This finding could be explained because

Propofol, Fentanyl, and Levophed use was significantly higher before closure of the abdomen compared to after closure. Depth of sedation has been found to be the main determinant of the oxygen consumption and resting energy expenditure index during the early postoperative period. After categorizing depth of sedation into three states according to the Ramsay Sedation Scale; increased depth of sedation has been shown to induce a progressive decrease in Vo2 and REE in postoperative mechanically ventilated patients.[4] Similarly, sedation alone has been reported to significantly decline energy expenditure. However, the administration of neuromuscular blockers to heavily sedated adults may have little effect on energy expenditure.[5, 6, 7, 8]

In contrast, the proportion of enteral feeding as well as pneumonia episode has been shown to be higher after closure of the abdomen. Feeding has a thermogenic effect that increases the vo2 and REE.[9, 10, 11] Uehara et al.[12] reported that during the first week after the onset of major trauma or sepsis, resting energy expenditure increased up to a maximum of 40% than normal REE, which might be because of the potential thermogenic effect of nutrition support and the hyper-metabolic response of the trauma or sepsis. Researchers reported that, by the third week of illness, REE was still greater than normal by $\geq$ 20%.

Along with the current study, several studies have shown that the presence of injuries and/or acute illnesses in hospitalized patients often alters REE values and metabolic response and therefore limits the accuracy of the predictive equations.[13, 14] For instance, the presence of fever, sepsis, and infection increased energy expenditure by up to 80% compared with normal controls.[15] Despite the fact that Frankenfield et al.[14] found sedated and medically paralyzed trauma patients to be impressively hypermetabolic and hyperdynamic, there have been few reports aiming to elucidate the factors that contribute to the successful prediction of REE.

Not only does the precise prediction of REE undertaken by predictive equations remain unclear, but also the presence of injuries and acute illnesses in hospitalized patients often alters metabolic response and limits the accuracy of predicated REE. These discrepancies may be explained by differences in severity of illness and changes in disease states over time, as well as by changes in the medical management of patients, especially those in the critical care setting. This is confirmed by our data that showed a weak agreement between measured and predicated REE by using Bland - Altman analysis.

Bruder et al.[6] showed that in sedated head-injured patients, body temperature and sepsis are responsible for most changes in energy expenditure. Moreover, the relationship between body temperature and energy expenditure that was found in sedated patients ($p = 0.0001$, $r^2 = 0.27$) was not found in non-sedated patients.

On the other hand, it is difficult to define precisely the effect of medical management on energy expenditure following acute illness, and especially in open abdomen situations, since multiple interventions such as morphine are commonly used.

Owing to the controversies faced by approaches to nutritional therapies, nutrition management of patients with an open abdomen remains a unique concern among surgeons and intensivists working in postoperative situations. Notably, no clear understanding exists regarding impact of the open abdomen on measured REE, due to changes in patient demographics and the complexities around patients being managed in hospitals.

The results of this review raises the question that variations of energy requirements before and after closure of the abdomen may need an aggressive nutrition support for specific phases of open abdomen patients when the enteral nutrition may be poorly tolerated.

Strengths and limitations

The present pilot study is the first to investigate the effect of open abdomen on resting energy expenditures and demonstrate potential factors that might affect REE measurements. The results of this study highlighted that nutrition targets have to be adjusted during the acute phase of stress, also in cases of ulterior deteriorations of clinical status. This includes new episodes of sepsis, or even adaptations to reduced nutritional needs.

Nevertheless, our study includes numbers of limitations associated with the small sample size. The size of the abdominal defect in the patients studied was not recorded; this introduces a potential bias since larger defects could pose an increased risk of hyper-metabolism and increased REE. However, the scope of this study was to examine the effects of the open abdomen technique on patients' resting energy expenditures during the same admission period. Furthermore, follow-up data on these patients after extubation or discharge from the ICU is lacking. Larger studies with sufficient power are needed to elicit these issues. The dose and effect of other medications such as morphine on REE has also not been investigated in this study.

CONCLUSIONS

In mechanically ventilated non-septic open abdomen trauma patients, the measured energy expenditure is not correlated to the abdominal status or sedation medications, but is dependent on body temperature while controlling other variables. The utility of indirect calorimetry as a standard of care tool is quite important in guiding nutrition targets and overcoming dynamic changes to energy requirements. Therefore, it has become necessary to scale nutritional needs with optimum targets to overcome the unparalleled feeding challenges that face open abdomen patients during the recovery phase.

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Table 1 – Patients' demographics

Demographics	Mean (n) / %
Age (years)	63
Duration of open abdomen (days)	5
Admission weight (Kg)	83
Gender	
Male	71
Female	29
Type of trauma	
Blunt	71
Penetrating	29

Table 2 – Univarinate analysis between REE measurements before and after closure of the abdomen

Variables	Before closure N=16	After closure N=15	P value
REE measurement (I.C)	1770 ± 415	2179 ± 381	P = 0.012
Penn State equation	1900 ± 390	1930 ± 329	P = 1.000
H-B equation	1624 ± 344	1706 ± 333	P = 0.696
REE/Penn	1	1.13 ± 0.354	P = 0.673
REE/H-B	1.06 ± 0.26	1.27 ± 0.46	P = 0.338
npRQ = RQ	1	1	P = 1.000
FiO2	45 ± 11	46 ± 7	P = 0.770
PEEP	8.6 ± 2.4	7.7 ± 2	P = 0.281
Temperature (median)	37.2 ± 0.45 (37)	37.9 ± 0.74 (38)	P = 0.027
Number of chest tubes (median)	(2)	(1)	P = 0.021
Richmond agitation sedation scale [RASS] (median)	(-1)	(0)	P = 0.529
Propofol	93% (15/16)	60% (9/15)	P = 0.033
Fentanyl	100% (16/16)	40% (6/15)	P = <0.0001
Levophed	56% (9/16)	20% (3/15)	P = 0.043
Dobutamine	25% (4/16)	0% (0/15)	P = 0.058
Pancuronium(Epidural)	6% (1/16)	20% (3/15)	P = 0.275
Tracheostomy	0% (0/16)	13% (2/15)	P = 0.226
Route of feeding			
- No feeding	75% (12/16)	33% (5/15)	P = 0.024
- EN	25% (4/16)	60% (9/15)	P = 0.053
Sepsis	0% (0/16)	13% (2/15)	P = 0.226
Pneumonia	0% (0/16)	27% (4/15)	P = 0.043

Table 3 – Bland - Altman analysis showing the agreement between mean measured and predicted REE

Comparisons	Mean difference	SD difference	Upper limit of agreement	Lower limit of agreement	Average between REE and value
REE and HB before closure	323.33	429.49	1182.32	-535.65	1338.5 and 2478.5
REE and HB after closure	537.45	399.52	1336.49	-261.59	1740.25 and 2357.25
REE and Penn state before closure	39.48	302.08	643.63	-564.68	1342.33 and 2634.5
REE and Penn state after closure	178.65	165.45	509.54	-152.24	1695.88 and 2513.25

Figure 1 – Distribution (pattern) of REE values before and after abdominal closure

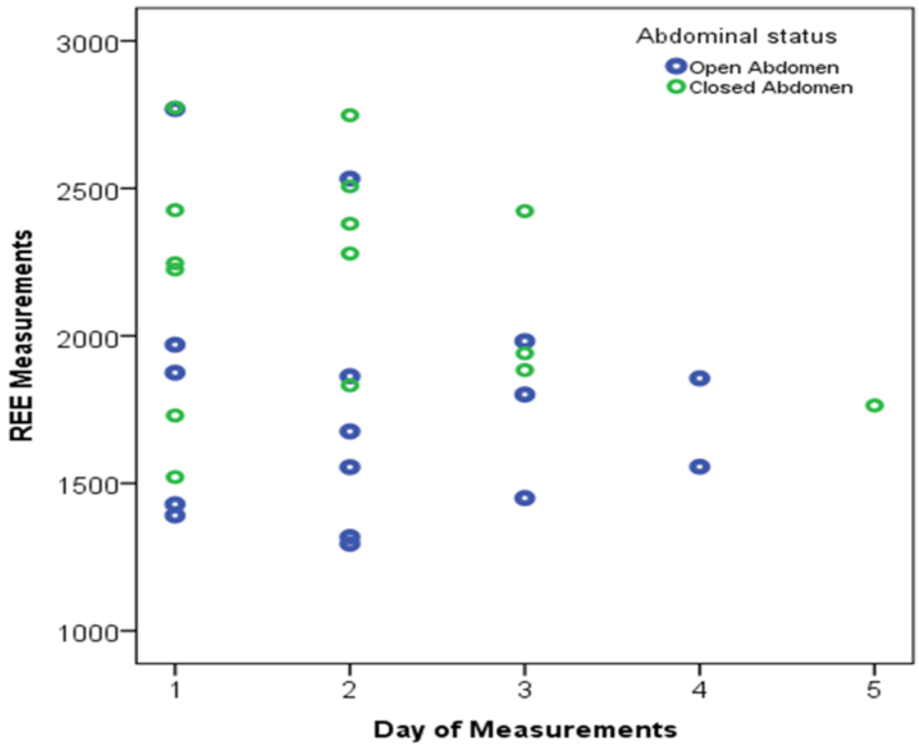


Figure 2 – Statistical analysis comparing variables with REE before and after abdominal closure

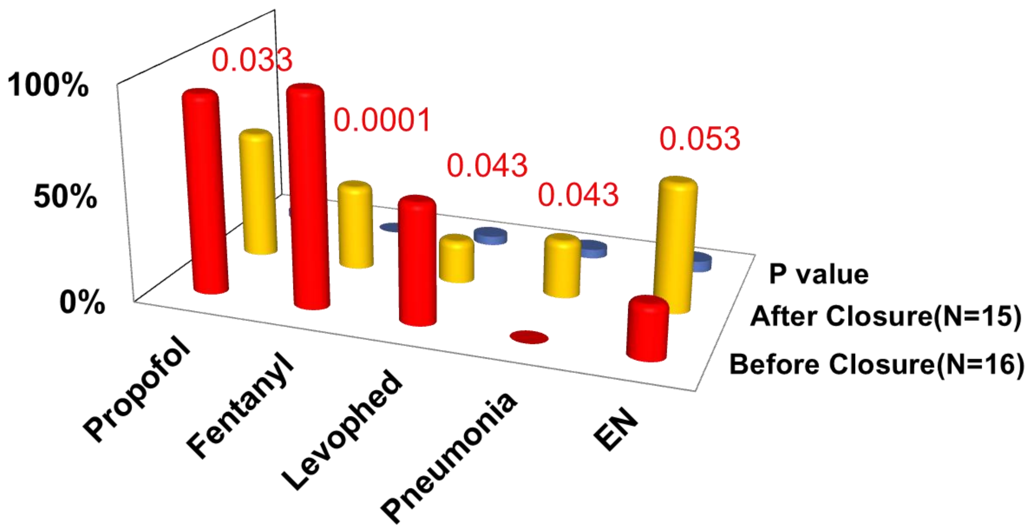


Figure 3 – REE values before and after closure of the abdomen

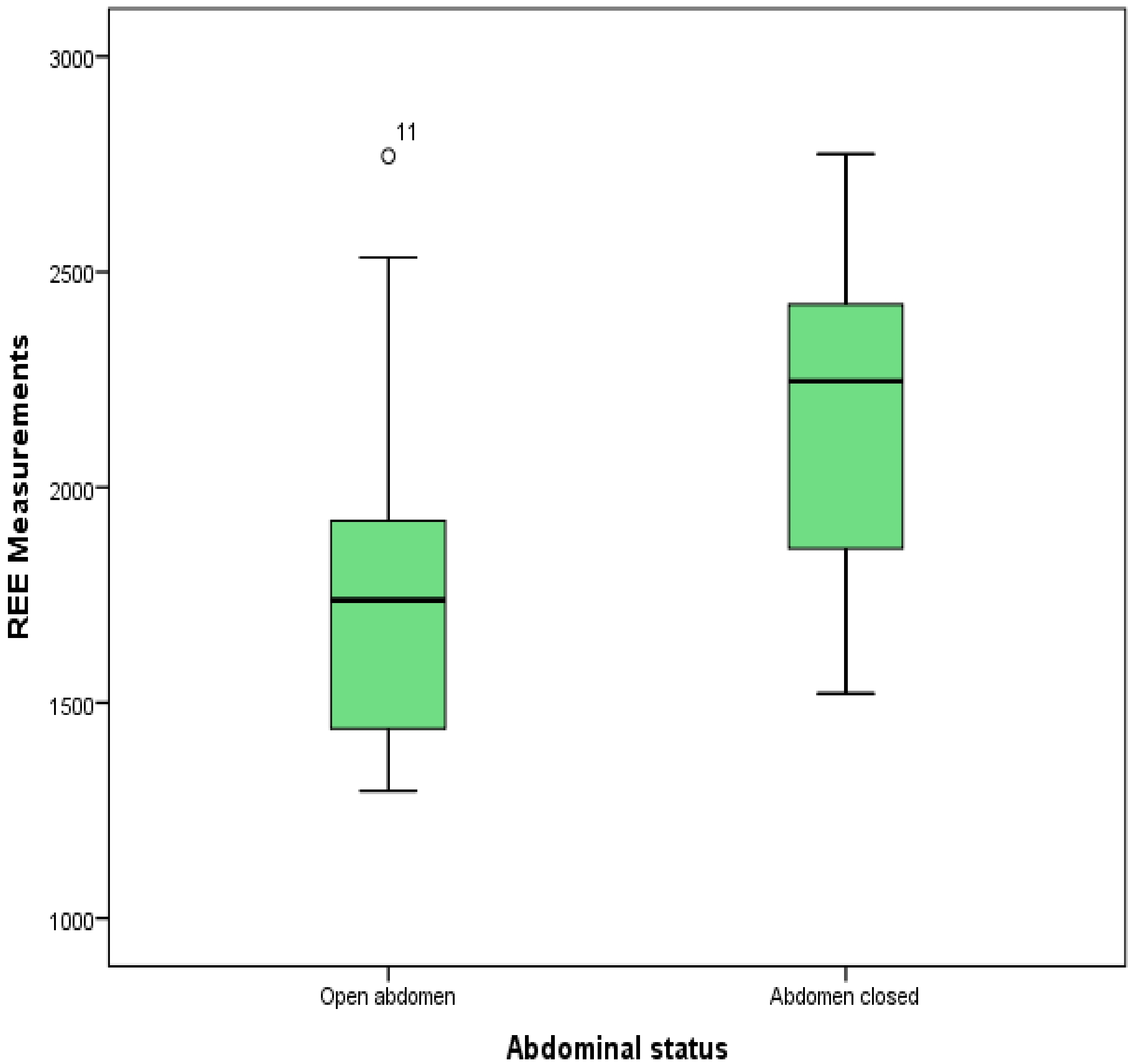


Figure 4 – Effects of Fentanyl on REE measurements

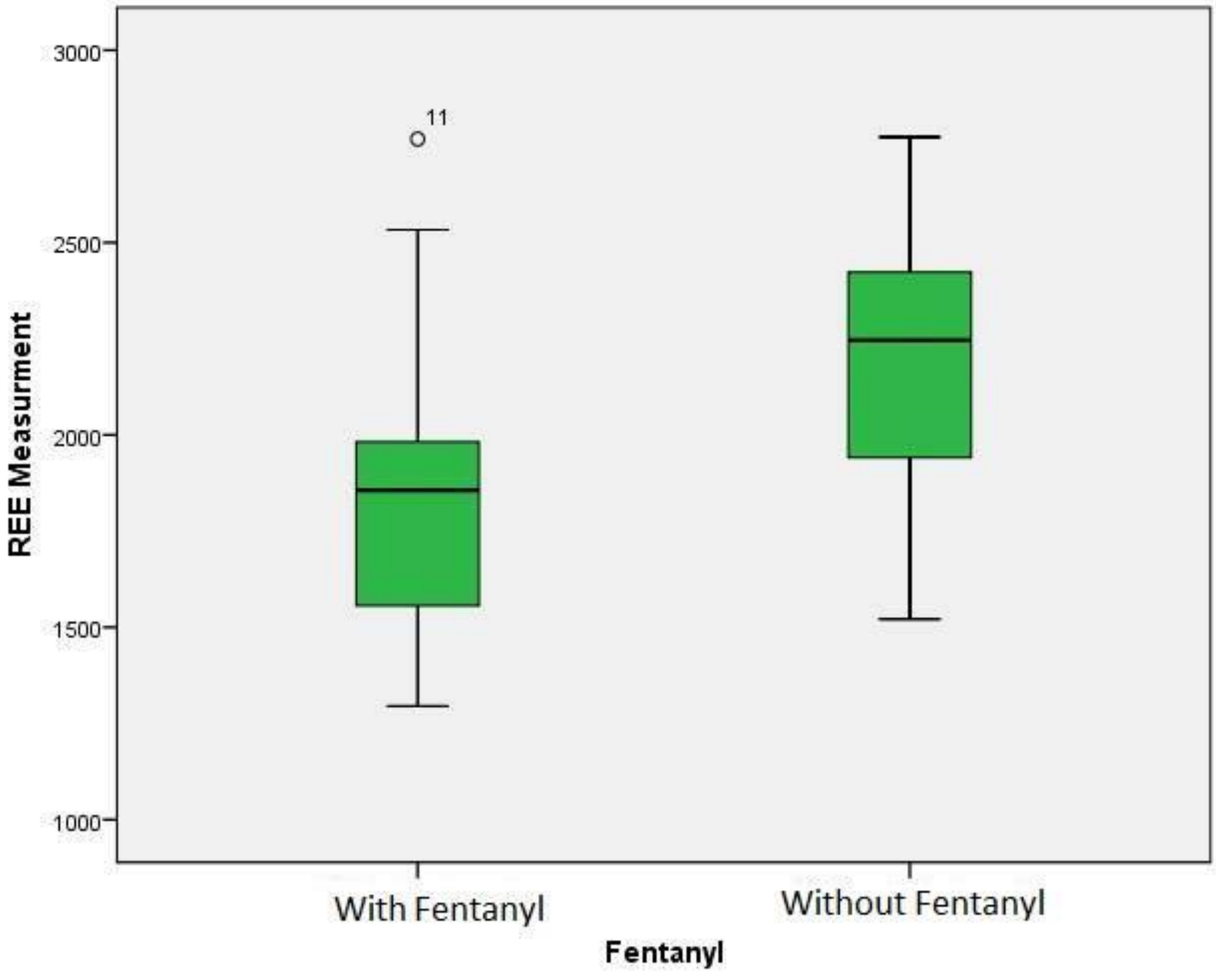


Figure 5 – Effects of Levophed on REE measurements

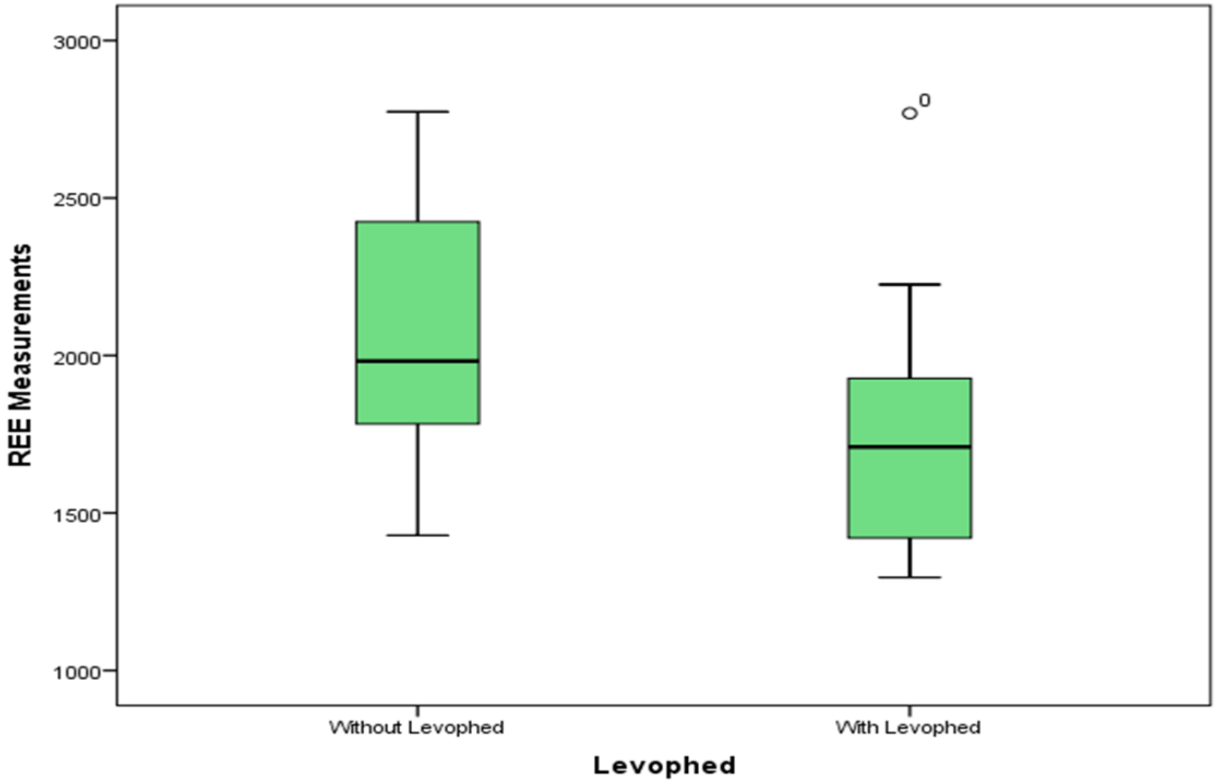


Figure 6 – Effects of Propofol on REE measurements

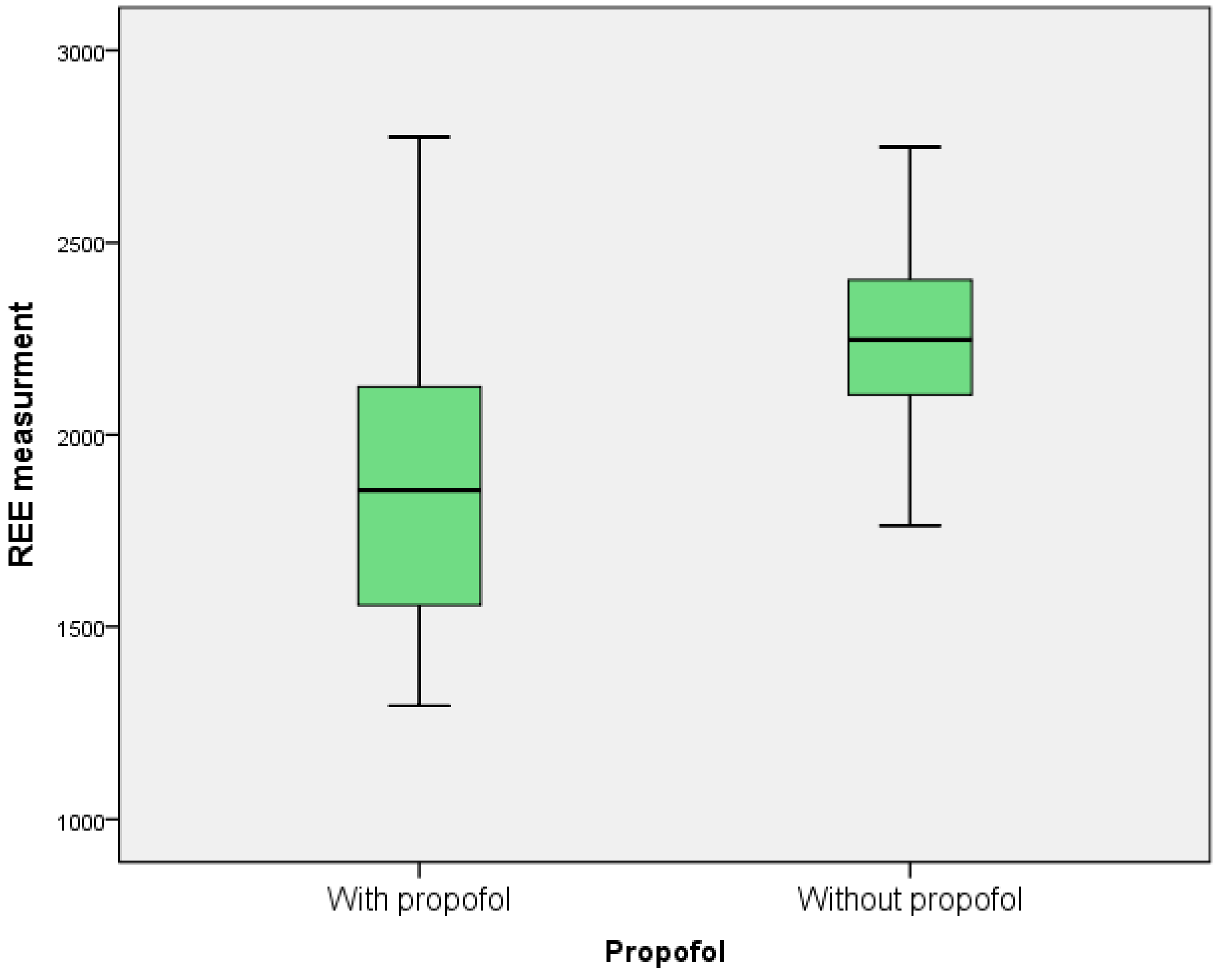


Figure 7 – Effects of feeding on REE measurements

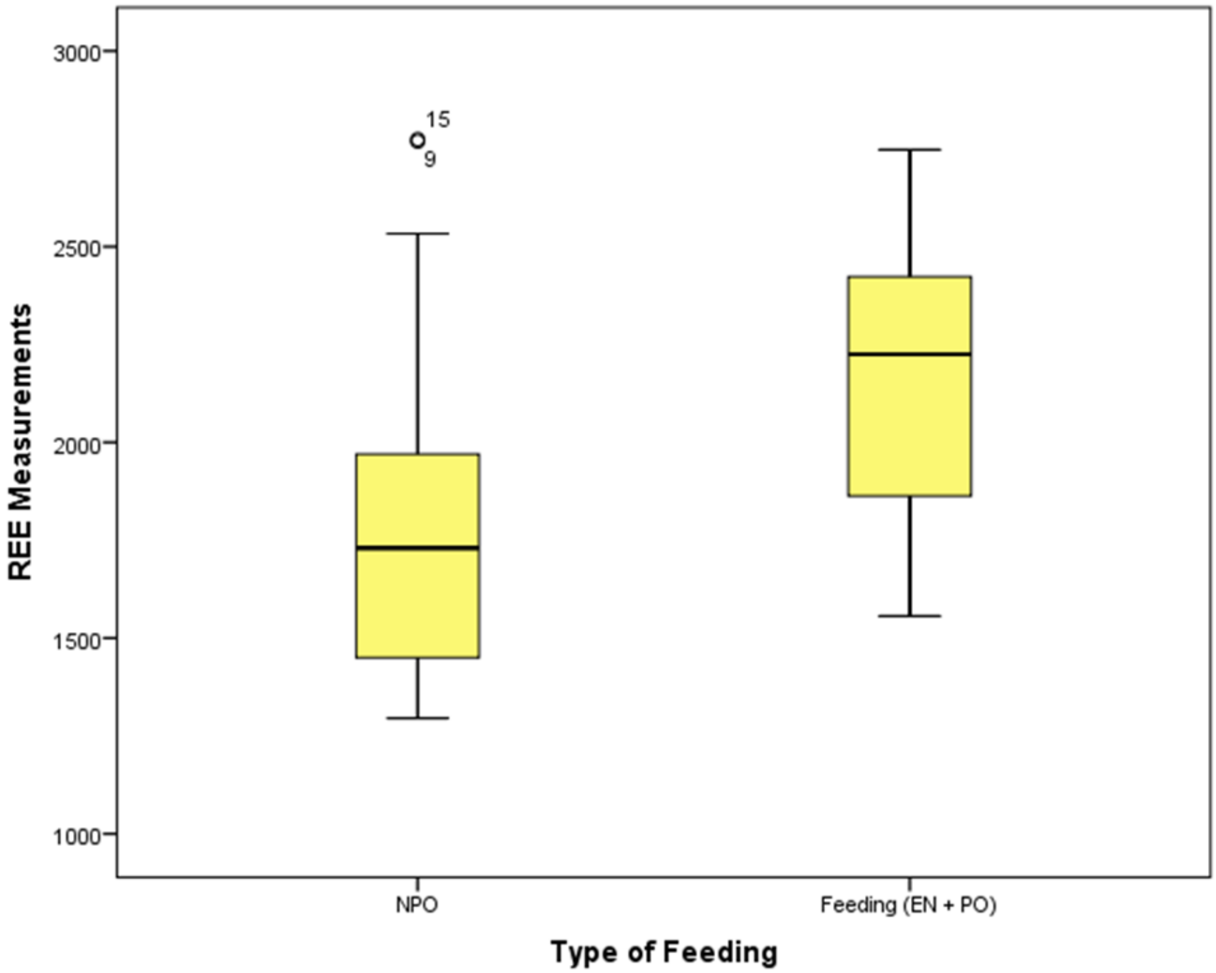


Figure 8 – Effects of Pneumonia on REE measurements

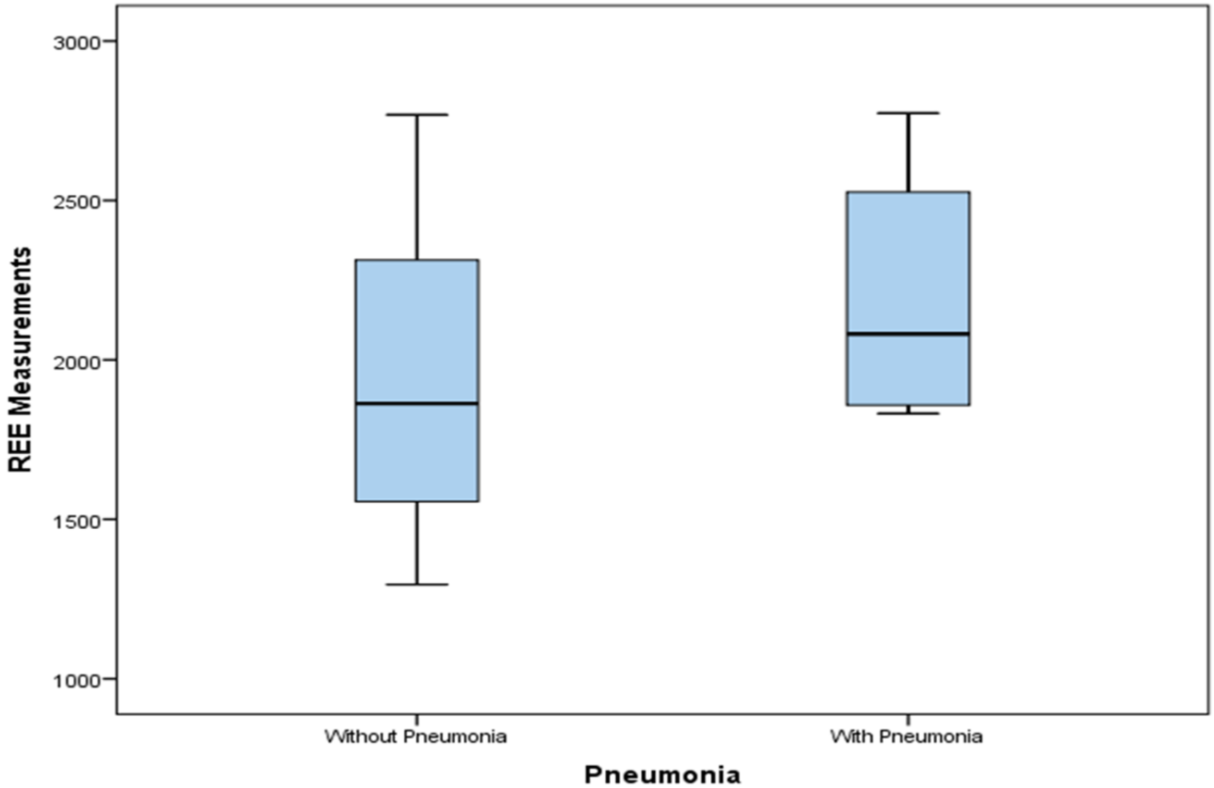
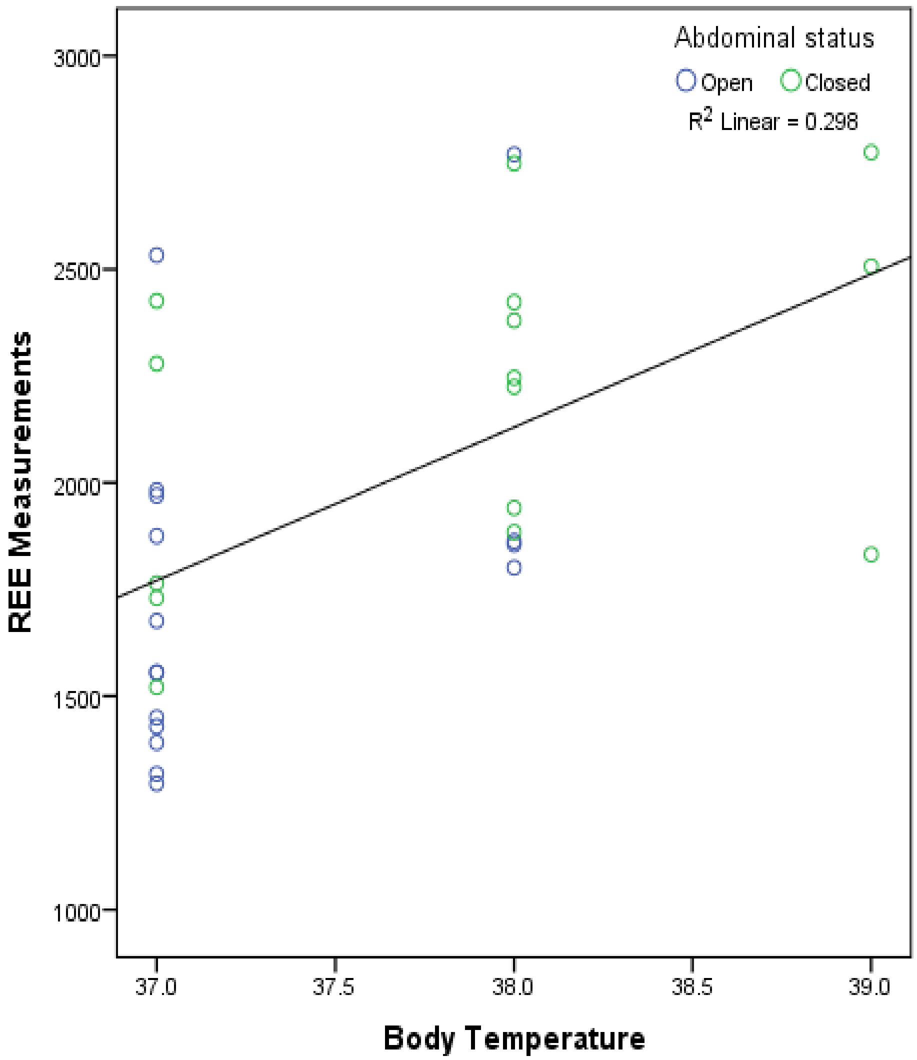


Figure 9 – Correlation between REE values and body temperature



5. GENERAL DISCUSSION

5.1 MAJOR FINDINGS

The aim of the thesis is to provide a comprehensive overview of nutritional assessment in subjects undergoing open abdomen surgery. Different outcomes were evaluated and measured in manuscripts A and B. In manuscript A, we investigated the adequacy of nutritional support and different clinical outcomes, mainly, survival over 14 ICU days for open abdomen patients who had an open abdomen for seven days or more after trauma or general surgery emergencies. In the manuscript B, we looked prospectively at the impact of open abdomen of REE values before and after closure of the abdomen. Also, we looked at the other potential factors that might affect REE measurements and differences between predicted and measured REE

In manuscript A, we observed that majority (91%) of those critically ill patients were insufficiently fed during their first two-week stay in the ICU. In the agreement with the conclusion of Hise and colleagues[(2)] that showed majority of medical and surgical ICU patients were underfed, with a minority exceeding 70% of goal requirements. Absences of strict feeding protocol and interruption of feeding were the main reason of underfeeding. Our patients often required multiple surgical interventions to repair orthopedic injuries, debridement of wounds and drainage of abscesses that could have led to feeding interruption and subsequently led to underfeeding. Other study showed that surgery and diagnostic procedures accounted for 42% of feeding interruption.[(108)]

In term of clinical outcomes, clinical outcomes such as sepsis, pneumonia, ICU length of stay, and duration of open abdomen were not statistically significant in both optimal and suboptimal calorie and protein groups. However, in the group who achieved $\geq 90\%$ protein target, unadjusted survival was found to be statistically significant (100% vs. 64%, P = 0.011). Moreover, in the second week, TPN use was higher in the group that achieved ≥ 90% of the protein target (P = 0.002). Improved 60-day survival was observed by Alberda et al.[107] when increasing both calorie intake and protein intake especially when the BMI <25 or ≥ 35. Previous study by Rao et al[100] found that provide 50% - 90% of the measured REE to mechanically ventilated patients can improve their protein nutritional status compared with general energy group (90 - 130% of measured REE). In contrast, in the Krishnan and colleagues [109]study, an energy intake more than 33% of the American Chest Physician recommendations for energy delivery was associated with higher death rates for the sickest ICU patients. Furthermore, in open abdomen study conducted by Dissanaike et al.[43] showed that immediate enteral feeding (within first 36 hours) has significantly less rate of pneumonia compared with non-immediate group (43.8% vs 72.1%, p = 0.008). However, no significant difference in mortality, length of ventilator days, ICU days or hospital days was seen between groups. Despite this study demonstrating that there is an increase in the first month albumin level which is expected, they did not look at the nutritional status or if these patients get the adequate nutrition therapy compared to the target. Thus, our data showed that in this selected population it is not necessary if you start the feeding early (≤ 4 days); they will reach the optimal goal during first 2 weeks especially if these had an open abdomen for at least 7 days.

On the other hand, our data demonstrate that achieving the optimum kcal in the second week did not seem to affect clinical outcomes. In contrast, prospective, randomized, single center, pilot clinical trial on adult general ICU conducted by Singer et al.[110] over 2 weeks that showed providing near target may be associated with lower hospital mortality. However, this was also associated with prolonged duration of mechanical ventilation and ICU stay. In agreement with other study that concludes that achieving 81% of goal requirements had extended hospital and ICU stays when compared with patients who received less nutrition.[2]

In addition to the current study, McClave et al.[111] has shown that only 25% to 32% of patients receive a nutrition support regimen that provides an amount of calories within 10% of their required needs.[111, 112]

The optimal amount of energy and protein required by critically ill patients to reduce morbidity and mortality is a matter of debate.[107] However, the persistent hypocaloric feeding and negative energy balances are associated with adverse outcomes which have been verified in the sickest critically ill patients.[106] Other study by Hise et al[2] concluded that most severely ill patient may not benefit from matching nutrient intake to goal recommendations during ICU stay.

The ultimate aim of nutritional therapy is to maximize the benefits of nutrition support and minimize complications where, it has become fundamental to serial mentioning REE to optimize energy perfusion in addition to maintain organs functionality. Because energy expenditure is difficult to predict on the basis of conventional equations, patients in acute care facilities are routinely overfed or underfed. Therefore, we conducted this pilot study to determine the effect of abdomen status and other potential variables that might affect REE measurements pre and post closure of the abdomen. Moreover we observed the differences between measured and predicated nutrition target in manuscript B.

In manuscript B, surprisingly, our study showed that the measurements of REE in open abdomen patients differ significantly after closure of the abdomen (1770 vs. 2179 kcal/day, P = 0.012). As was discussed, during the study period, REE measurements changed before and after closure of the abdomen due to different potential factors such as sedation and body temperature.

The results of our study present a preliminary evaluation of impact of open abdomen of REE values and factors that may lead to a change in REE needs after and before closure of the abdomen among open abdomen patients who were at 2 weeks of inadequate feeding as was observed in the manuscript A.

Our studies demonstrate that multiple factors may have caused differences between measured REE before and after closure of the abdomen. The hyper-metabolic state, depth of sedation, medications, body temperature and sepsis were found to be the main determinant of resting energy expenditure during the early postoperative period.

Use of the metabolic cart precisely to determine the nutritional needs enables the physician to design the most efficacious nutritional target. Thus, it remains unclear if changing REE and hyper-metabolism are present only before closure of the abdomen, or whether these characteristics are also found after closure of the abdomen in conjunction with changes in patient demographics and the complexities involved in patients being managed in hospitals.

Moreover, the present study highlighted that determination of REE by predicative equations cannot predict accurately resting energy requirements in this group of patients. According to the study results, the agreement between the measured and predicted REE was weak. In fact, the Penn state and the Harris-Benedict equation may underestimate energy requirements post closure of the abdomen, while it might overestimate energy needs before closure of the abdomen based on Penn state prediction.

Similarly, Koukiasa et al.[113] reported that spontaneous intracranial hemorrhage patients were in hyper-metabolic state during the 10 first post-hemorrhage days, with a mean REE equal to 117.5% of the basal metabolic rate (BMR). REE increased over time (P = .077), reaching significance (P < .005) after the seventh day (126.4% BMR). Moreover, compared with predicted REE by using Harris-Benedict equation, the measured REE was increased significantly in all the studied points (p<0.005).

Several authors have examined the relationship between energy expenditure and body temperature. Of the four trial, a positive correlation was reported in one study (r = 0.44, p < .01)[114] and no association was reported in three studies.[115, 116] There was an association found between temperature and energy expenditures reported for subjects with a greater severity of head injury,[116] brain death,[117] and those receiving sedation, and/or sepsis. Fever increased energy expenditure by approximately 10% per degree of Celsius, and sepsis increased energy expenditure independently of fever.[81]

An interesting aspect of this study is that sedation was not correlated with the measured REE. A similar observation was also pointed out by Koukiasa et al.[113] who reported no correlation was identified between REE and depth of sedation, as well as Acute Physiology and Chronic Health Evaluation II, Glasgow Coma Scale, and Hunt and Hess scores. However, a significant correlation also was found between REE and temperature (P = .002, r = 0.63) on the first 10th day post intracranial hemorrhage.

This variation in energy expenditure could occur because of the difference between patient populations with different disease states, and due to the fact that each individual has and may demonstrate a unique metabolic response to a given injury. Unfortunately, those patients with a greater severity of critical illness are the ones with the greatest variation in energy expenditure.

The results of manuscript B highlighted that indirect calorimetry seem to be a more reliable approach and valid tool for assessing REE in the open abdomen population. Findings also indicated that measured REE differ significantly before and after closure of the abdomen. As induced stress by transient increase of intra-abdominal pressure may create new ebb and flow phase that could deteriorate the nutritional status. Furthermore, this pilot study supports the utility of indirect calorimetry as an assessment tool for tailoring REE in open abdomen patients, as it may better guide optimal nutritional targets. To add to the results of several other studies,[118-120] differences between measured and calculated energy expenditures were observed which make the predicative equations not an accurate way to determine the energy requirements during the acute phase of illness.

Our data demonstrates that underfeeding is common in open abdomen patients who are critically ill because of multiple factors, such as sedation, feeding, and body temperature, which are associated with changes in measured REE both before and after abdominal closure. On the other hand, it might due to inaccurate determination of energy target by using the predictive equations.

When put together with individual patient's characteristics, indirect calorimetry can guide clinicians or institutes in daily clinical practice. Ultimately, careful monitoring of REE may be quite important and may lead to better nutrition care and guide nutritional targets.

5.2 STRENGTHS AND LIMITATIONS

The results of the present study highlight the need for more research in this area in order to optimize nutrition support for open abdomen populations. Further research could contribute to making optimization more feasible and decrease the need to rely on inaccurate equations while providing appropriate energy requirements. This study has attempted to characterize the correlations between abdomen status, body temperature, measured REE, sedation and nutrition provision in mechanically ventilated non-septic patients following an acute open abdomen surgery.

Manuscript A discussed findings that showed open abdomen patients were insufficiently fed, especially during a specific period, specifically when the patients had an open abdomen for seven days or more. This review had several limitations. This study was limited to a small sample size and was of a retrospective nature. Also, no assessment was performed in this study to identify the outcomes after discharging form the ICU. The patients were mix of trauma and general surgery emergencies, the size of abdominal defect were not recorded which might create bias as the larger defect might loses larger amount of fluids and nitrogen and lead to malnutrition. There is a lack of nutritional marker data at the admission time. Moreover, the most common causes of underfeeding in this population are still unclear. Especially, these patients had an increase of nitrogen losses form the abdomen cavity that is usually uncounted, resulting to more protein depletion

On the other hand, the strength of manuscript B was in the prospective and rigorous nature of the data collection. This study is unique, as assessed prospectively REE before and after closure of the abdomen for any trauma patients who are sedated, mechanically ventilated, non-septic after laparotomy. The same researcher performed the measurements and collected the data prospectively. The treating team was also blinded to the primary intervention. However, this study limited to small sample size (only 7 patients) and short time interval only 7 days pre and post closure of the abdomen. Three patients had only one measurement before closure of the abdomen. There were limitations related to measurement and steady state, as the measurements were postponed until the patient was at a steady state (PEEP less than 12, and FiO_2 less than

60%). Despite most of the measurements were carried out at the first three days of the ICU admission, timing of the measurements were based on the patient's clinical stability which introduces a selection bias.

5.3 FUTURE DIRECTIONS

Indirect calorimetry technology is relatively expensive, and in most centers it is still viewed as a research tool. No study has yet proven that we should implement indirect calorimetry as a standard component of patient care. Moreover, questions regarding the daily use of this tool remain with no clear answer.

The results reported in this thesis may be used in future trials with patients undergoing open abdomen or temporary abdominal closure surgery not only to selectively include patients at a high risk of malnutrition, but also to use IC as a standard of patient care. Further research should investigate whether measuring REE precisely before and after closure of the abdomen will improve post-operative outcomes. The results of this thesis highlight the need for more research in this area

Currently there is no standard or consistent method for assessing nutritional status in open abdomen population. Therefore, we conducted a national survey as a first step for capturing current nutritional practice and provide a "snap shot of the daily practice" of open abdomen patients admitting to ICU to elucidate factors that influence the risk of energy intake deficiency. (See appendices)

Although nutrition administration has improved over the years in terms of skills, materials, and formula, larger studies are needed to identify the major barriers to adequate nutrition intake in critically ill adults, and to identify optimal protein and calorie needs with an optimum target

5.4 CONCLUSIONS

To our knowledge, this thesis is the first to demonstrate that open abdomen patients, with an open abdomen for seven days or more, are underfed. Patients who achieved ≥ 90% of the protein target were found more likely to survive. Measured REE was shown to change dynamically pre and post closure of the abdomen. Furthermore, the utility of indirect calorimetry was proven to make it an important and essential practical tool; thus, it is proposed that indirect calorimetry could be used as a standard of care in ICUs, instead of the current reliance on inaccurate predictive equations. Patients experiencing an acute surgical procedure such as the open abdomen technique are at a high nutritional risk and require special attention. A large-scale clinical trial is necessary to correlate the abdominal status with overall REE needs.

6. APPENDICIES

6.1 Feeding Practices of Open Abdomen Patients: National Survey

Feeding Practices of Open Abdomen Patients

The purpose of the survey is to examine the experience and preferences of different specialities that manage the patient with an open abdomen in the context of nutrition assessments
For the purpose of this survey, an open abdomen patients will be defined as any patient with an open fascia as well as with an open skin. Patient is consider as closed either when the fascia is closed or when the fascia left open with skin closure or with skin graft.

* 1. How many years have you been in clinical practice?

- ◯ <5 years
- ◯ 5-10 years
- ◯ 11-15 years
- ◯ 16-20 years
- ◯ >20 years

* 2. On average, how many open abdomen patients do you manage annually?

- ◯ <5
- ◯ 6-10
- ◯ 11-15
- ◯ 16-20
- ◯ >20

* 3. Please choose all specialties that apply to your practice?

- [ ] General surgery
- [ ] Trauma surgery
- [ ] Hepatobiliary surgery
- [ ] Colorectal surgery
- [ ] Transplant surgery
- [ ] Internal medicine
- [ ] Anesthesia
- [ ] Critical care
- [ ] Clinical nutrition
- [ ] Other (please specify)

* 4. Do you work in a hospital with a "closed" ICU unit model (Intensivist managing/co-managing the patient) ?

- ◯ Yes
- ◯ No

5. Please indicate your primary practice setting ?

- ◯ University/academic Hospital
- ◯ Community Hospital (university-affiliated)
- ◯ Community Hospital (not affiliated with university)
- ◯ Urban Hospital (not affiliated with university)
- ◯ Urban Hospital (university-affilliated)

Other (please specify)

Feeding Practices of Open Abdomen Patients

* 6. On average, when do you start using ENTERAL feeding in open abdomen patients (unless contraindicated)?

- 0 - 24 hrs.
- 24 - 48 hrs.
- 2 - 4 days
- > 4 days
- Rarely

* 7. While the patient is still opened, on average when do you start using PARENTERAL nutrition in open abdomen patients?

- 0 - 24 hrs
- 24 - 48 hrs.
- 2 - 4 days
- > 4 days
- Rarely

* 8. What is your initial route of feeding in open abdomen patients during ICU stay?

- Full Enteral Nutrition
- Trophic Enteral Nutrtion
- Total Parenteral Nutrition (TPN)
- Peripheral Parenteral Nutrition (PPN)
- Combined (Enteral+Parenteral)

* 9. While considering parenteral feeding in open abdomen patients, what is the likelihood of starting parenteral feeding in the following situation below ?

	Very Unlikely		Neither Likely or Unlikely		Extremely Likely
Hemodynamic instability	◯	◯	◯	◯	◯
Bowel injury / intestinal discontinuity	◯	◯	◯	◯	◯
Stoma	◯	◯	◯	◯	◯
Ileus / bowel obstruction	◯	◯	◯	◯	◯
Duration of open abdomen	◯	◯	◯	◯	◯
Likelihood the patient will be closed in the near future	◯	◯	◯	◯	◯

* 10. In your hospital, how are the nutritional requirements assessed ?

- ☐ Metabolic cart (indirect calorimetry)
- ☐ Penn sate equation
- ☐ Harris-Benedict equation
- ☐ Swinamer equation
- ☐ I don't know
- ☐ Other (please specify)

* 11. If the metabolic cart (indirect calorimetry) is used, how often do you use it in open abdomen patients?

- ◯ Every day
- ◯ Once a week
- ◯ Twice a week
- ◯ I don't use the metabolic cart
- ◯ I don't know
- ◯ Other (please specify)

* 12. When the nitrogen balance is calculated, do you consider the protein loss from the abdominal fluid to estimate the protein needs?

- ◯ Yes
- ◯ No
- ◯ I do not know

* 13. During the ICU admission, please estimate the percentage of patients achieving the optimal caloric or protein target?

	< 10 %	10 - 25 %	26 - 50 %	51 - 75 %	> 75 %
Optimal **caloric** target **before** closure of the abdomen	◯	◯	◯	◯	◯
Optimal **caloric** target **after** closure of the abdomen	◯	◯	◯	◯	◯
Optimal **protien** target **before** closure of the abdomen	◯	◯	◯	◯	◯
Optimal **protien** target **after** closure of the abdomen	◯	◯	◯	◯	◯

* 14. In your opinion, how will the abdominal closure affect the following ?

	Will increase / improve	No change / the same	Will decrease / decline
Resting Energy Expendetuire (REE)	◯	◯	◯
Protien needs	◯	◯	◯

* 15. Please rate your level of agreement with the following statements?

	Strongly Disagree	Disagree	Neither Disagree Nor Agree	Agree	Strongly Agree
If not contraindicated, **early enteral feeding** (less than 4 days) is safe and feasible in open abdomen patients	○	○	○	○	○
Early enteral feeding has positive clinical outcomes in open abdomen patients	○	○	○	○	○
If indicated, **early parenteral feeding** is safe and feasible in open abdomen patients	○	○	○	○	○
Early parenteral feeding has positive clinical outcomes in open abdomen patients	○	○	○	○	○
Achieving the optimal **caloric** target has postive impact on open abdomen patient's outcomes	○	○	○	○	○
Achieving the optimal **protien** targert has postive impact on open abdomen pateint's outcomes	○	○	○	○	○
The metabolic cart (Indirect Calorimetery) is a feasible/effective tool to optimize the nutritional needs in open abdomen patients	○	○	○	○	○

* 16. Among open abdomen patients, please rate your level of agreement with each factor could lead to inadequate feeding

	Strongly Disagree	Disagree	Neither Disagree Nor Agree	Agree	Strongly Agree
Delays and difficulties in obtaining EN or TPN access	◯	◯	◯	◯	◯
Patient has bowel injury	◯	◯	◯	◯	◯
Resuscitate and stabilize the patient take priority over nutrition	◯	◯	◯	◯	◯
Lack of agreement among ICU Team	◯	◯	◯	◯	◯
Waiting for the dietitian to assess the patient	◯	◯	◯	◯	◯
Patient is not tolerating the feeding (Nausea, vomiting, high residual volume)	◯	◯	◯	◯	◯
Lack of tracking and calculating the nutrition intake	◯	◯	◯	◯	◯
Other complication e.g aspiration pneumonia	◯	◯	◯	◯	◯

Table 1 – Indication for use of open abdomen technique as per Diaz et al. review and as per levels of recommendations

Level of Recommendations	Abdominal Compartment Syndrome (ACS)	Damage Control	Emergency General Surgery	Vascular Surgery
Level I	Yes	No	No	No
Comments	All patients with ACS, defined as intra-abdominal pressure (IAP) 20 mm Hg (with or without an abdominal perfusion pressure (APP) 60 mm Hg—World Congress of ACS [WCASC] definition), manifested as organ dysfunction (abdominal distension, decompensating cardiac, pulmonary, and renal dysfunction) should undergo emergent decompressed laparotomy			
Level II	Yes	Yes	Yes	Yes
Comments	-An acute increase of intra-abdominal pressures to 25 mm Hg, ACS is likely and	-In the cases of severe abdominal trauma because of penetrating or blunt injury involving	-The DC and open abdomen technique may be considered for patients with severe intra-	-The DC and open abdomen technique should be considered after rAAA in significant

	decompressed laparotomy and an open abdomen technique should be considered	hepatic, non-hepatic, or vascular injuries with intra-abdominal packing, - the use of the OA technique should be considered, and an early decision to truncate a definitive operation should be made as soon as possible	abdominal infection/peritonitis. -Source control remains the major predictor of outcome	visceral edema where abdominal closure would result in ACS
Level III	Yes	Yes	Yes	Yes
Comments	- After DC of non-abdominopelvic trauma, IAP should be monitored as secondary ACS can occur after either massive transfusion or massive fluid resuscitation - Open abdomen management should be considered in the following clinical circumstances to prevent ACS: transfusion of 10 units of red blood cell (RBC) and fluid resuscitation 15 L of crystalloid	-DC and the OA technique should be considered if the following clinical parameters are reached: acidosis (pH 7.2), 2-hypothermia (temperature 35°C), clinical coagulopathy and or if the patient is receiving massive transfusion (10 units packed RBCs)	-The DC and open abdomen technique may be considered in the management of severe necrotizing pancreatitis	-The DC and open abdomen technique should be considered after rAAA in IAH of 21 mm Hg in postoperative rAAA

Table 2 – Levels of recommendations according to Diaz et al. review

Levels of Recommendations	Definition
Level I	This recommendation is convincingly justifiable based on available scientific information alone. It is usually based on class I data; however, strong class II evidence may form the basis for a level I recommendation, especially if the issue does not lend itself to testing in a randomized format. Conversely, weak or contradictory class I data may not be able to support a level I recommendation.
Level II	This recommendation is reasonably justifiable due to available scientific evidence and strongly supported by expert opinion. It is usually supported by class II data or a preponderance of class III evidence.
Level III	This recommendation is supported by available data but adequate scientific evidence is lacking. It is generally supported by class III data. This type of recommendation is useful for educational purposes and in guiding future studies.

Table 3 – Definition and grading of intra-abdominal hypertension

Definition of IAH	Normal IAP* is approximately 5–7 mm Hg in critically ill adults.[121] IAH* is defined by a sustained or repeated pathologic elevation in IAP ≥ 12 mm Hg
Grade I	IAP 12–15 mm Hg
Grade II	IAP 16–20 mm Hg
Grade III	IAP 21–25 mm Hg
Grade IV	IAP > 25 mm Hg
* IAH - Intra-abdominal Hypertension * IAP - Intra-abdominal Pressure	

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