

# **Peritoneal vacuum therapy to reduce the systemic inflammatory insult from intra-peritoneal sepsis/injury/hypertension: A randomized comparison of baseline wall suction versus the KCI AbThera™ Abdominal Dressing**

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## **Introduction**

The abdominal compartment syndrome (ACS) is generally defined as a state of serious organ dysfunction resulting from sustained increases in intra-abdominal pressure (IAP), that most obviously affects the cardiovascular, respiratory, and renal systems(1-6). It is uniformly fatal if untreated. Although the physiology of the ACS, which requires the initiation of severe intra-abdominal hypertension (IAH), was conceptualized and described over 100 years ago, interest in this syndrome has only recently been rekindled(7). This reawakening is evidenced in the establishment of an international scientific society dedicated to understanding these processes, the World Society of the Abdominal Compartment Syndrome (WSACS) ([www.wsacs.org](http://www.wsacs.org)), as well as an exponential increase in the annual number of publications on this subject(8). With renewed interest and study, these entities are being increasingly recognized in settings and patients that were previously unsuspected and thus missed. In an effort to standardize definitions and facilitate communication and research, the WSACS has thus outlined working definitions, standardized techniques for IAP measurement, and compiled initial evidence-based guidelines for the diagnosis, management, and prevention of IAH and ACS(9, 10). The WSACS recently defined IAH as a consistently elevated IAP greater than 12 mmHg, with four distinct grades(9). When IAH becomes severe, it culminates in an overt clinical syndrome representing an life-threatening pattern of altered physiology and organ failure that may affect nearly all organ systems(11).

IAH and ACS are most commonly recognized in high risk situations such as damage control surgery for trauma and after major abdominal vascular procedures(12-14). It has also become apparent that any patient undergoing aggressive resuscitation after shock is subject to the

risks of IAH and the ACS even without the presence of primary abdominal pathology (2, 15, 16), and this is an independent predictor of mortality(16). IAH and the occurrence of ACS has not only been recognized in a wide variety of clinical settings, but have been noted to be relatively common if sought with vigilant monitoring.

Severe sepsis is a leading cause of death in ICUs throughout the world, with mortality rates reaching 30%, and an ever increasing estimated number of cases per year approaching 18 million worldwide per year(17-20). Sepsis is characterized by reduced perfusion, global tissue hypoxia, and when severe, organ dysfunction. Patients with intra-abdominal infections are perceived to be at risk of elevated IAP both as a result of the primary intra-peritoneal disease, as well as the massive fluid resuscitation often required to maintain organ perfusion(14, 21, 22). Despite data suggesting over 750,000 annual presentations of severe sepsis, there is a relative paucity of data regarding the occurrence of IAH/ACS in this group(18). What is known however is alarming both in the potential scope of the problem as well as the general ignorance of the problem. Recent studies have demonstrated a high prevalence of IAH following aggressive resuscitation of septic patients. Intra-abdominal hypertension is present in as many as 80% of septic medical and surgical ICU patients(23, 24). Reintam also reported that septic patients with IAH had a 50% rate of mortality compared to 19% without IAH, making IAH a significant marker for an increased risk of death(25). Within our own institution, rates of IAH were over 87% of septic ICU patients and further 61% of these patients had severe IAH at levels commensurate with ACS, despite the fact that IAP was only measured in 10% of the patients in whom guidelines recommend monitoring (McBeth, unpublished data).

Intra-abdominal sepsis (IAS) is a particularly devastating and common place form of sepsis(26, 27). Despite improved surgical techniques, supportive critical care, and new antimicrobials, the mortality still remains as high as 25%, with much morbidity in survivors(28, 29). While the medical community remains generally blinded to the issue of IAH/ACS occurring within the symptom complexes/pathophysiology of IAS, these conditions are inseparably intertwined. It has been well established that visceral ischemia is both a precipitating and complicating factor in both shock and multi-organ failure(30, 31), and that ACS induces severe visceral ischemia among other consequences(2, 32). There is a complex relationship between pressure, ischemia, and inflammation within the peritoneal cavity. Independently the damaged gut seems to act as a continued source of inflammation propagating SIRS and potentiating MODS(33-35). Although extremely complicated, visceral ischemia further characteristically generates multiple immunological mediators with the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin six (IL-6), as well as inhibitive cytokines such as interleukin ten (IL-10)(36-39). Post-operative complications associate with increasing levels of systemic IL-6, and peritoneal TNF-  $\alpha$ (38, 40). Jansson and colleagues believe that peritoneal cytokines in humans respond more extensively compared to systemic cytokine, and that a normal postoperative course is characterized by decreasing levels of peritoneal cytokines based on studies of both elective and emergency surgery(41). Overall, the peritoneal cytokine response is much higher than the systemic response in peritonitis(39, 42-44). In a series of rat studies, Hendriks and colleagues demonstrated that peritoneal cytokine levels (especially IL-6, TNF-  $\alpha$ , (27)and IL-10) were dramatically different in rats who either survived or succumbed to an intra-peritoneal sepsis model in the 24 hours after cytokine determination(42). Finally, recent work

suggests that blood filters designed to hemofiltrate blood endotoxins and cytokines may improve hemodynamics, organ dysfunction and even mortality in the critically ill(45-48).

Despite immense time and resources being dedicated to develop and test innumerable pharmaceutical and biologic interventions to alleviate the ravages of the septic syndrome, only one, activated protein C, has shown sustained promise; but despite early enthusiasm the therapy remains controversial and the indications uncertain(49). Therefore the cornerstones of treating sepsis remain supportive care, timely source control typically involving surgical or percutaneous drainage, and antimicrobial therapy.

Therefore, given the immense burden of suffering and limitations of our current pharmacotherapy, physical therapies continue to be actively investigated. It is increasingly understood that inflammatory mediators perpetuate systemic inflammation and MODS. It is thus logical to attempt to remove these mediators to ameliorate the local effects and to prevent there being absorbed systemically. Although early uncontrolled work suggested benefit to simple continuous peritoneal lavage after either gross peritoneal contamination in secondary peritonitis or in the setting of necrotizing pancreatitis(50, 51), more structured studies could not confirm such benefits(52-54). Thereafter work focused upon using hemofiltration to remove inflammatory mediators from the blood which has been associated with decreased hypercytokinemia (as assessed by blood IL-6 levels), early improvements of hemodynamic state and decreased lactate levels(55-57). In an attempt to comprehensively increase efficiency, the potential utility of adding extra-corporeal mediator removal through hemofiltration in addition to continuous peritoneal lavage have been entertained and studied in early models(48).

Active peritoneal vacuum therapy may be a more direct and focused solution to this complicated problem. Whether improved post-operative courses can be obtained through this relatively simpler approach of actively removing peritoneal cytokines with a more efficient and comprehensive VAC therapy in humans is therefore attractive but currently unstudied in humans and thus is the rationale for this study.

This rationale relates to the fact that the peritoneal cytokine response to peritonitis and abdominal inflammation has been shown to be much greater than the systemic(39, 41, 43, 44). Benchtop studies suggest that the newer AbThera dressing is markedly more efficient and comprehensive in providing vacuum therapy to the peritoneal cavity (Delgado AV, unpublished)(Appendix A). More importantly, recent animal studies have suggested that peritoneal vacuum therapy is remarkably simple and efficacious in both managing the open abdomen, and ameliorating the systemic damage occurring from IAS. A recent porcine study by Kubiak and colleagues(58), demonstrated reduced intestinal, pulmonary, renal, and hepatic histopathology, reduced systemic inflammation as reflected by significantly reduced levels of TNF- $\alpha$ , IL-1 $\beta$ , IL-6), as well as reduced IAP, improved cardiac and renal function, and improved pulmonary compliance, in a porcine IAS model that was randomized to either passive intra-peritoneal drainage or vacuum drainage(58). Overall, by utilizing the active vacuum therapy, there were marked improvements in most organ systems within the thoracoabdominal cavity. Lung compliance was improved with reduced peak and mean airway pressures and a lower (although non-significant) occurrence of acute lung injury (ALI) from 66 to 33% was noted. Further, the cardiac outputs were increased, urine outputs improved, intestinal edema reduced, and even the mortality in the active therapy group was 17% versus 50%(58).

These remarkable results, although globally beneficial across multiple organ systems, still raise questions as to mechanism. The specific methodology of this trial leaves it uncertain whether the mechanism of benefit relates to the authors hypothesized mechanism of draining inflammatory ascites, or possibly related to a decrease in IAP which would subsequently increase visceral perfusion and improve manometric-related pressures through-out all body cavities(59), or possibly a combination of these mechanisms, or some other unknown one. It has also been shown in animals that IAH itself activates primed neutrophils and constitutes a second hit propagating lung and liver damage in the setting of MODS(60). Nonetheless, the profound and system wide improvements in this critical disease warrant urgent evaluation of this therapy in critically ill humans.

This trial will be constructed as a hypothesis generating pilot study while it will thus asses a variety of outcomes, no formal power calculations will be conducted. In general, others have hypothesized that cytokines, especially peritoneal levels, are sensitive indicators of the post-operative inflammatory reaction and may predict complications(41). In experimental models IL-6 levels are higher in non-survivors(42, 44). Further, previous work has noted that the blood level of IL-6, which has a longer half life than TNF- $\alpha$  or IL-1 $\beta$ , is a good index of the overall cytokine cascade activation(61, 62). Thus the main outcomes to be compared will be between mean cytokine levels measured in each of the two treatment groups.



## **Local practice at the Foothills Medical Centre**

A randomized trial of utilizing or not, active intra-peritoneal vacuum therapy is practical and would not compromise patient care or clinical therapy at the Foothills Medical Centre. Currently, although the AbThera is approved and used there is great uncertainty and certainly equipoise regarding the timing and indications for its use. Although the current Department of Critical Care Medicine, clinical-practice-guidelines (CPGs) for sepsis, recommend attention to the issue of IAH/ACS, these guidelines are extremely poorly followed. The decision to leave an abdomen open is typically made quite arbitrarily and there is no current standard or protocol as to what exact criteria or thresholds mandate or warrant this potentially life-saving but potentially morbid complicated approach. Nonetheless our research group has tried to address these questions and has previously lead multi-institutional research collaboration for the Trauma Association of Canada in beginning to address these questions(63, 64).

Typically, once the decision has been made to employ the OA technique surgeons at FMC typically employ a local modification of the home-made “Barker VAC-pac”(65, 66), which involves a polyurethane bag opened to protect the bowel with or without a towel next, which is thereafter covered with a large opsite™ dressing (Appendix B). Typically, one or two Jackson-Pratt™ drains are left inside the dressing to drain ascitic fluid. For the purposes of this study this will be designated as the “Stampede VAC”. Although the necessity of such is poorly known, temporary abdominal closures are typically changed in a 24-96 hour time-frame, after which, if the surgeon feels it is still not safe (based on subjective and ill-defined criteria) to formally close

the abdomen, a commercial VAC<sup>TM</sup> dressing will typically be placed, which will thereafter also be changed every 48-96 hours.

## **Intervention**

Patients requiring an open abdomen (OA) for either critical illness or injury who require admission to the multi-disciplinary critical care unit of FMC will be randomized (Figure 1.) to either;

- a) Calgary-home-made- (“Stampede VAC”) with only closed drain bulb suction  
(Appendix B, Figure 2)

or

- b) AbThera vacuum assisted abdominal closure at 125 mmHg suction (Figure 3)

The time that the dressing will be left in place, will be left to the discretion of the attending surgeon, but revised practice guidelines (Appendix C) mandate either formal abdominal closure or dressing change at 24-96 hours from placement. Only those patients who have had an OA for at least 24 hours will be eligible for assessment of the physiological outcomes (see below and Appendix D), while all patients will have the global outcomes assessed regardless of the time that the OA was in place (see below). Upon the first OA dressing change, the surgeon is free to utilize whatever temporary closure they choose, noting that the Trauma Services guidelines recommend use of the commercial KCI VAC dressing (Appendix C).

Just prior to placement of the first dressing, 16 ml of blood will be drawn from an existing arterial or venous line (this will qualify as Day 1). The same quantity of blood will be drawn on days 2, 3, 7 and 28 (or hospital discharge, whichever comes first). 50ml of peritoneal fluid will also be collected from the abdomen on the same days or until closure of the abdomen and removal of the dressing. Peritoneal fluid is drained from the abdomen and usually discarded. We will take the fluid present in the collection receptacle which will be of absolutely no inconvenience to the patient.

### **Inclusion Criteria**

- 1) Critically ill/injured requiring intensive care unit admission
- 2) Decision regarding the need to utilize an open abdomen technique after the first laparotomy
- 3) Age  $\geq$  18
- 4) Non-pregnant

### **Exclusion Criteria**

- 1) Decision to formally close the abdomen after the initial laparotomy
- 2) Pregnancy
- 3) Age  $<$  18

## **Physiological Outcomes**

All patients who are managed for at least 24 hours with either vacuum drainage (intervention) or the passive drainage (control) will be eligible for assessment of physiological outcomes which will include, but won't be limited to:

### a) Primary Outcomes

- i) Systemic inflammatory marker levels (e.g. TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-10)
- ii) Peritoneal fluid inflammatory marker levels (e.g. TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-10)

### b) Secondary Outcomes

- i) Determination of the type and activation status of inflammatory cells present in the peritoneal fluid.
- ii) Measurement of the activation potential of peritoneal fluid
- iii) Peritoneal fluid drainage volume
- iv) Post-operative fluid balance
- v) a) Mean 24 hour intra-abdominal pressure (IAP)
- v) b) daily WSACS IAH grading classification
- vi) SOFA score and individual organ system components of the score
- vii) PaO<sub>2</sub>/FiO<sub>2</sub> ratio
- viii) Oxygenation Index
- ix) Vasopressor Requirements
- x) RIFLE score
- xi) Need for renal replacement therapy
- xii) APACHE II score
- xiii) Mean 24 hour lactate level

xiv) Mean 24 hour enteral tolerance (if no anastomosis)

### **Global Secondary Outcomes**

- i) In-hospital Death (recognizing the trial will not be powered to detect a meaningful difference)
- ii) Days with fascial closure for the month after admission
- iii) Ventilator free days for the month after admission
- iv) ICU free days from the month after admission
- v) Hospital free days from the month after admission
- vi) Days free of renal replacement therapy from the month after admission

### **Other Baseline and Follow-Up Variables**

**1) Demographic data:** age, gender, pre-existing and co-morbid medical conditions including, but not limited to, respiratory, cardiac, endocrine, and neurological diseases, Sabadell modification of the McCabe score regarding underlying conditions and known comorbidities before the OA(67).

**2) Admission injury/illness severity data:** mechanism of injury or illness, Injury Severity Score (ISS)(68-70), Anatomic Injury Scores (AIS), Revised Trauma Score (RTS)(68, 69), Glasgow Coma Score (GSC)(70-72)

**3) Physiologic and laboratory data:** mean arterial pressure, heart rate, white blood cell count, neutrophils count, platelets count, base deficit, type and site of infection (if present) and arterial blood gasses, requirements for inotropic support, requirements for mechanical ventilation.

## **Statistical Issues**

This novel trial will be conducted as a pilot, with the philosophy of potentially enabling a research program aligned with the Alberta Sepsis Network to study both the basic science and treatment options for the peritoneal response to intra-abdominal inflammation. Thus, this practical exploratory trial will not be powered to detect high level clinical outcomes such as death which would typically require larger multi-centre trials although this work will hopefully constitute part of the necessary preparation to justify such future endeavors.

Although, all enrolled patients will be analyzed on an intention to treat basis, a planned post-hoc analysis will consist of a stratified analysis of outcomes in traumatic versus non-traumatic cases of the open abdomen.

## **Recruitment Issues**

While an open abdomen may be necessitated by an innumerable variety of potential circumstances, the majority of cases relate to serious intra-abdominal injuries, inflammatory intra-peritoneal conditions, or the secondary abdominal compartment syndrome. Patient who thus require open abdomen management are largely primarily attended to by surgeons from either the Division of General Surgery and/or Regional Trauma Services at Foothills Hospital. Typically there are approximately 2 to 10 patients a month that require this therapy, with trauma experiencing peak numbers through the summer and general surgery being relatively stable through-out the year. A conservative estimate of recruitment is therefore 2 patients per month. The study will be conducted for 2 years with a goal of recruiting 40 patients. All of these

patients will unfortunately be completely incapacitated at the time that an immediate decision to initiate the course of an “open abdomen” will have to be taken. All these patients will be fully anesthetized at this time point, as well as further incapacitated requiring full life-support due to the inciting condition(s) mandating an OA. Further, even if next of kin are available in the hospital, the surgical team will be fully engaged in performing life-saving surgery/resuscitation and delay to obtain informed consent for the study would be impractical if not dangerous. Thus, the only practical approach to consent will be to obtain delayed consent from the patient upon recovery. There are no known side effects or negative consequences of the standard therapy, only anticipated benefits of the novel therapy. All general/trauma surgeons taking call at the FMC are expected to be familiar and facile at using either dressing technique otherwise they should not be on call at the FMC. In-services and consultations will be conducted prior to beginning the study however to ensure the quality and standard of dressing placement.

## **Randomization and Data Collection**

Randomization shall be through a treatment allocation generator hosted on the research page of the Trauma Association of Canada website ([http://www.traumacanada.org/research\\_committee/](http://www.traumacanada.org/research_committee/)). This site is freely open to the public and can be accessed by any junior member of the surgical/anesthesia/critical care medicine/nursing team, thus freeing the senior surgeon to concentrate on care. When an appropriate patient is recognized, the research site will be accessed, simple identifiers of the patient will be entered, and treatment allocation (standard “Stampede VAC” application or AbThera KCL dressing) associated with this entry will be generated. To ensure close balance of the numbers in each of

the two treatment groups a variable block size randomization will be used. Thereafter, all care will be at the complete discretion of the clinical teams. Full data collection and completion of the data forms will be collected and completed by the Research support staff of Regional Trauma Services with possible assistance of the Department of Critical Care Medicine.

## **The Research Team and Prior Relevant Research**

This project aims to take advantage of two research programs that are currently active at the University of Calgary. The team of Dr. Paul Kubes, director of the Calvin, Phoebe and Joan Snyder Institute of Infection, Immunity and Inflammation and Chair of the Snyder Translational Laboratory in Critical Care Medicine, is world famous for their work on leukocyte recruitment in sepsis, a critical step in the defense of the host against invading organisms. Dr. Kubes is also a founding member of the Alberta Sepsis Network, an Alberta Innovates Health Solutions funded team grant focusing on the development of new science and technology which will serve to uniquely understand this devastating disease and help in the design of successful clinical trials

The Intra-abdominal Hypertension/Abdominal Compartment Syndrome research team led by Dr Andrew Kirkpatrick, has also been active in researching this entity for over 10 years, and hopes to lever the elegant basic science of Dr Kubes team to assist with their practical surgical knowledge. The surgical critical group has previously studied/described methods of diagnosis and measurement of IAP(5, 15, 73-80), studied it's bedside interpretation(81-84), as well as extensively reviewed the literature(2-4, 74, 85-87). Further, members of our research group sit on the Executive Committee of the World Society of the Abdominal Compartment



Syndrome and have co-authored Society-based consensus documents and statements(9, 10, 88, 89).

## **Acknowledgements**

**Anita Verdonk RN BScN CEN ET, Clinical Therapies Specialist KCI Medical Canada, Inc.**

for review of the proposal and technical information.

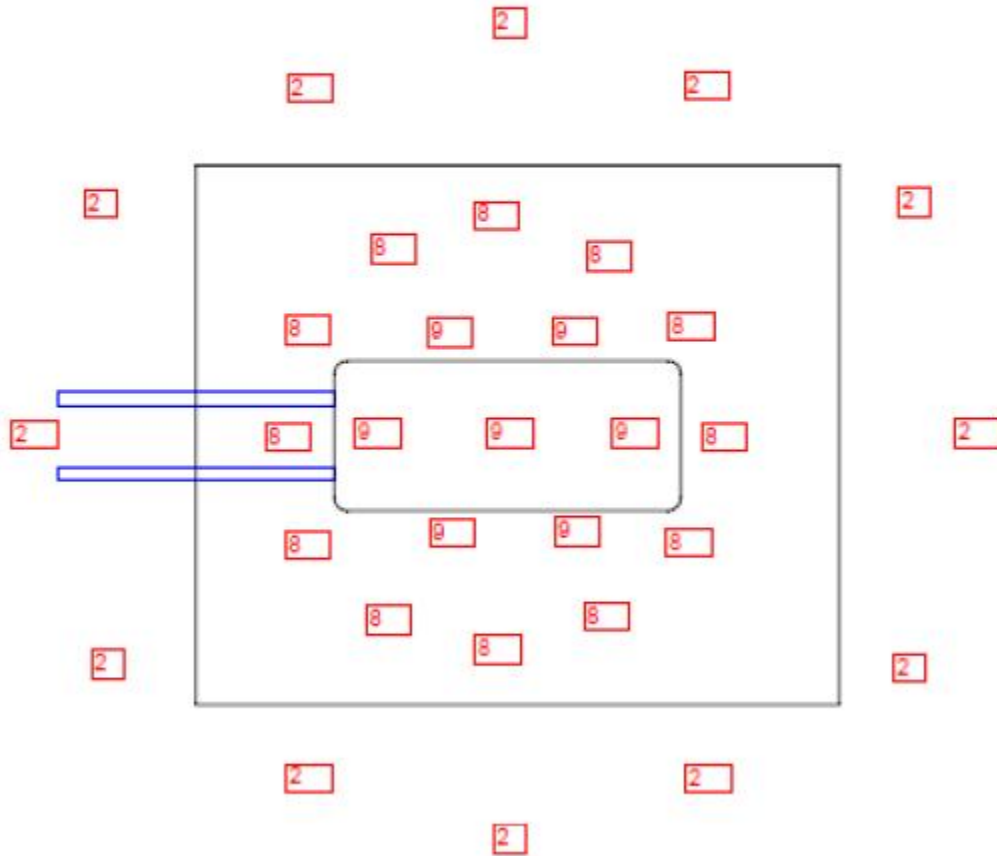
**Angel Delgado PhD, KCI Medical, San Antonio, Texas.**

for technical information.

## **Appendices and Figures**

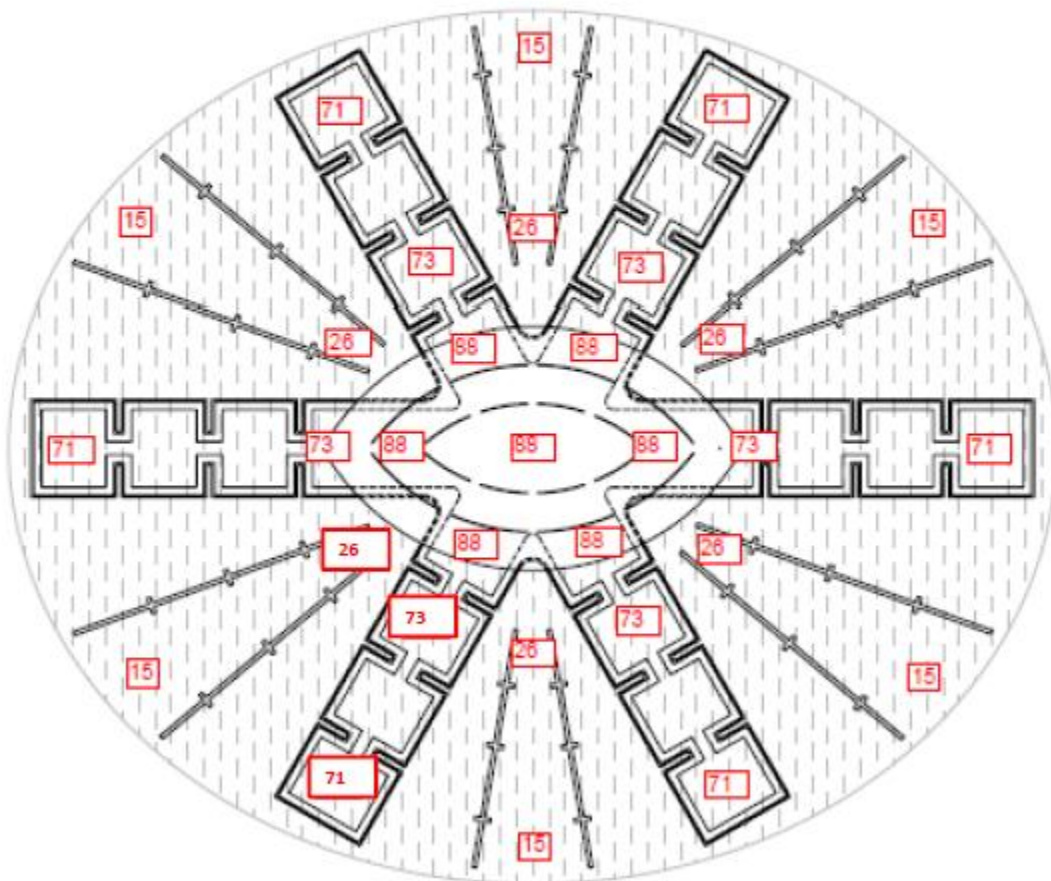
- Appendix A**            **Physical characteristics of Model TAC dressings**
- Appendix B**            **Definition and Protocol for use of the Calgary-home-made “Stampede VAC”**
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- Figure 1.**                **Flowchart of Study Overview**
- Figure 2.**                **Typical Calgary home-made “Stampede VAC”**
- Figure 3.**                **AbThera Commercial VAC in use at Foothills Medical Centre**

# Barker's



**Legend** Vacuum pressures within a simulated temporary abdominal closure in a benchtop model (courtesy Delgado AV, unpublished data, KCI Corporation)

# ABThera™



**Legend** Vacuum pressures within a simulated temporary abdominal closure in a benchtop model (courtesy Delgado AV, unpublished data, KCI Corporation)

## **Appendix B**

### **Definition and Protocol for use of the Calgary-home-made “Stampede VAC”**

#### **Supplies Required**

One - Sterile Radiology Cassette drape (make, manufacturer)

Two – Jackson-Pratt drains

Two – Large Opsite™ sterile sheets

Six – glass vials of Mastasol

One – green surgical sponge (optional)

#### **Procedure**

##### **The recommended procedure for utilization of the “Stampede VAC”**

- 1) Ensure sterility of all steps at all times
- 2) Open the cassette drape to its entire size by cutting the seams
- 3) Completely cover the bowel with the cassette drape by underlaying the drape under the edges of the abdominal wall and extending as far down into the para-colic gutters as possible and up over the liver and deep within the pelvis as possible
- 4) Place two JP drains into the space superficial to the cassette dressing brought out through a tract through the skin lateral to the incision bilaterally, taking care to avoid the fascia
- 5) If the surgical sponge is to be used it is now placed superficial to the cassette drape
- 6) Remove the surgical retractors (if any) and surgical drapes from the field

- 7) Dry the skin of the abdomen and chest well
- 8) Apply Mastasol liberally to the skin
- 9) Apply the Opsite™ dressing over the entire wound
- 10) Activate the JP bulbs to provide suction

(This protocol is also available at;

<https://my.calgaryhealthregion.ca/http://iweb.calgaryhealthregion.ca/programs/trauma/pdf/Regional%20Trauma%20Services%20Open%20Abdomen%20Policy%20.pdf>)

## **Appendix C – Regional Trauma Services Guidelines and Recommended Protocol for the Management of the Open Abdomen**

The indications for leaving the fascia open after a laparotomy are multiple and exceptions to any rule or protocol, that are based on sound surgical judgment are to be expected(63, 64).

An OA may also be necessitated by a number of clinical conditions both elective and emergent(90, 91). It may be an unplanned but accepted consequence of either wound dehiscence after laparotomy or the catastrophic loss of the abdominal wall integrity from necrosis, tumor, or trauma(90, 92). It may also be a planned strategy in anticipation of re-exploration, peritonitis management, or to decompress the primary, secondary, or recurrent abdominal compartment syndromes(9, 75, 91, 93).

### **Protocol**

- 1) The decision to close or not close the fascia is a surgical decision to be made by the responsible attending trauma surgeon, but should reflect the careful consideration of all clinical and physiological parameters and suggestions of other involved critical care physicians (such as anesthesia or critical care medicine).
- 2) In the absence of a clinical trial, the suggested initial dressing is the Calgary home-made VAC pac modification of the dressing originally described by Barker(65, 66), hereafter referred to as the “Stampede VAC” (see Appendix B).
- 3) If the Stampede dressing is not utilized however, a fundamental principal is to AVOID suturing the fascia if a planned re-laparotomy is intended.



- 4) Any stomas placed should be constructed as laterally as possible to allow the application of advanced abdominal dressings
- 5) Any “Stampede VAC” is intended to be removed or changed within a 24 – 96 hour time frame. Shorter durations between re-operation are most appropriate when the patient improves quickly physiologically or does deteriorate or swell when the OA was utilized as a largely prophylactic measure. Longer time durations are appropriate, though when the patient remains critically ill, swollen, and has not had resolution of the ongoing physiologic issues.
- 6) The intra-abdominal pressure is an important parameter that must be measured in all OA patients, in order to guide decision-making regarding re-laparotomy timing and to maintain surveillance against tertiary IAH \ ACS(3, 5, 15).
- 7) In any patient who has had sponges left within the peritoneal cavity, or for whom an emergency count was required, formal radiographs of the peritoneum (including the high thoraco-abdominal regions and the deep pelvis) are required in addition to a thorough exploration at laparotomy to document the absence of a retained foreign body (in accordance with regional policies).
- 8) If the physiology is improving, and thoracoabdominal pressures are acceptable (airway pressures, IAP, hemodynamic indices) attempts at either formal closure or partial closure of the fascia are encouraged.
- 9) During secondary attempts at closing the fascia in OA patients, intraoperative IAP monitoring and close communication with the anaesthetist is warranted and recommended.

- 10) Permanent Prosthetic meshes should NOT typically be used in the acute closure setting of an OA, which is considered a non-sterile procedure, but this area warrants future scientific study.
- 11) The acute use of a bioprosthetic mesh, or of a component parts separation technique ARE acceptable opens for formal closure but this area warrants future scientific study.
- 12) If the fascia is not safe to formally close at reoperation upon an OA, the use of a commercial high vacuum suction dressing (KCI-VAC type dressing) is recommended, which should be changed every 48-96 hours until the fascia can be formally closed.
- 13) If despite aggressive efforts to close the fascia, the situation prevents this, the timing of a split-thickness skin graft with an intended future abdominal wall reconstruction remains an acceptable (although less desirable) option. The appropriate time for this should be decided by the attending surgeon in consultation with a consultative plastic surgeon.

## Appendix D

## Detailed Definitions of Physiological Outcomes Variables

<b>Systemic inflammatory marker levels (e.g. TNF-<math>\alpha</math>, IL-1<math>\beta</math>, IL-6, IL-10)</b>	Inflammatory mediators present in blood that are released as a response of the body to infection or injury. In sepsis the level of these mediators are markedly higher than the normal level. Reference - (94)
<b>Peritoneal fluid inflammatory marker levels (e.g. TNF-<math>\alpha</math>, IL-1<math>\beta</math>, IL-6, IL-10)</b>	Inflammatory mediators present in the peritoneal fluid that are released as a response of the body to infection. The concentration of these markers in the peritoneal fluid is higher in the presence of peritoneal sepsis. Reference (94)
<b>APACHE II score</b>	Acute Physiology and Chronic Health Evaluation score. Measure of the severity of disease for adult patients, based on 12 acute physiologic variables (Table D1), age (Table D2), and chronic health status (Table D3). The APACHE II score is determined by totaling points from these 3 sections, resulting in a total score between 0 and 71 points. APACHE II Score=Acute Physiologic Score+ Age Points+ Chronic Health Points. Points are assigned based on the most deranged physiological variables during the initial 24 hours in ICU. Higher scores imply a more severe disease and a higher risk of death. Reference - (95)
<b>SOFA score</b>	Sepsis related Organ Failure Assessment. Describes organ dysfunction/failure, computed based on respiratory, coagulation, cardiovascular, GCS, liver and renal variables (Table D4). Reference - (96)
<b>FiO<sub>2</sub>/PaO<sub>2</sub> ratio</b>	Index to characterize the acute respiratory distress syndrome
<b>Oxygenation Index</b>	(FiO <sub>2</sub> * Mean Airway Pressure) / PaO <sub>2</sub>
<b>RIFLE score</b>	Risk, Injury, Failure, Loss and End-stage renal failure score. Defines and stages acute kidney injury based on creatinine value increase and decrease in glomerular filtration rate (GFR) of urine output (Table D5). Reference - (97-99)
<b>IAP</b>	Intra-Abdominal Pressure. Pressure concealed within the abdominal cavity; expressed in mmHg. Normal IAP is ~ 5-7 mmHg in critically ill adults.
<b>IAH</b>	Intra-Abdominal Hypertension. Sustained or repeated pathologic elevation of IAP $\geq$ 12 mmHg. IAH is graded as follows: Grade I: IAP 12-15 mmHg, Grade II: IAP 16-20 mmHg, Grade III: IAP 21-25 mmHg, Grade IV: IAP $>$ 25 mmHg. Reference - (9)

Table D1

**Acute Physiologic Score (APS)**

Physiologic Variable	Score	High Abnormal Range			Normal			Low Abnormal Range		
		+4	+3	+2	+1	0	+1	+2	+3	+4
<b>Temperature</b> (Rectal/Core) Oral: add 0.5°C Axilla: add 1.0 °C		≥ 41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤ 29.9
<b>Mean Arterial Pressure</b> (mmHg)		≥ 160	130-159	110-129		70-109		50-69		≤ 49
<b>Heart Rate</b>		≥ 180	140-179	110-139		70-109		55-69	40-54	≤ 39
<b>Respiratory Rate</b> Non-ventilated or ventilated		≥ 50	35-49		25-34	12-24	10-11	6-9		≤ 5
<b>Oxygenation</b> a) FiO <sub>2</sub> ≥ .5, record AaDO <sub>2</sub>		≥ 500	350-499	200-349		< 200	AaDO <sub>2</sub> : [FiO <sub>2</sub> x713]-[PaCO <sub>2</sub> ÷0.8]- PaO <sub>2</sub>			
b) FiO <sub>2</sub> < .5, record only PaO <sub>2</sub>						> 70	61-70		55-60	< 55
<b>Arterial pH</b>		≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
<b>Serum Sodium</b> (mmol/L)		≥180	160-179	155-159	150-154	130-149		120-129	111-119	<110
<b>Serum Potassium</b> (mmol/L)		≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
<b>Serum Creatinine</b> (µmol/L)	*	≥309	177 - 308	132-176		53-131		<53		
*DOUBLE SCORE FOR ARF										
<b>Hematocrit</b> (%)		≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
<b>WBC</b>		≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
<b>GCS</b> (Score=15 minus actual GCS)		Enter Actual GCS here _____								
<b>*HCO<sub>3</sub></b> (Venous mMol/L) (*Only if no ABG)		≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15
<b>TOTAL PHYSIOLOGIC SCORE</b>										

Reference - (95, 100)

**Table D2**

<u>Age Points</u>	
Age (years)	Points
<=44	0
45-54	2
55-64	3
65-74	5
>=75	6

**Table D3**

<u>Chronic Health Points</u>	
Non-operative or emergency postoperative patients	5 points
Elective postoperative patients	2 points
No history of severe organ dysfunction or immune compromise	0 points

**Table D4**

<u>SOFA score</u>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
Respiration PaO <sub>2</sub> /FiO <sub>2</sub> mmHg	<400	<300	<200 ---with respiratory support---	<100
Coagulation Platelets X 10 <sup>3</sup> /mm <sup>3</sup>	<150	<100	<50	<20
Liver Bilirubin, mg/dl (umol/l)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (>204)
Cardiovascular Hypertension	MAP<70 mmHg	Dopamine<=5 or dobutamine (any dose)	Dopamine>5 or epinephrine<=0.1 or norepinephrine<=0.1	Dopamine>15 or epinephrine>0.1 or norepinephrine>0.1
Central nervous system GCS	13-14	10-12	6-9	<6
Renal Creatinine, mg/dl (umol/l) or urine output	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (>440)

Reference - (96)

**Table D5**

<b><u>RIFLE Category</u></b>	<b><u>Glomerular Filtration Rate</u></b>	<b><u>Urine Output Criteria</u></b>
Risk	Increased serum creatinine X 1.5 or decrease of GFR >25%	<0.5 mL/Kg/hr for 6 hrs
Injury	Increased serum creatinine X 2 or decrease of GFR >50%	<0.5 mL/kg/hr for 12 hrs
Failure	Increased serum creatinine X 3 or decrease of GFR >75% or serum creatinine $\geq$ 4mg/dL	<0.3 mL/kg/hr for 12 hrs or anuria for 12 hrs
Loss	Complete loss of renal function for >4 wks	
End-stage kidney disease	Need for renal replacement therapy for >3 mos	

References - (97-99)

## Appendix E

## Detailed Definitions of other baseline and follow-up data

<i>Demographic data</i>	
<b>Sabadell modification of the McCabe score</b>	A predictive score that reflects a subjective prognosis of each patient at discharge, based on the subjective perception of the attending intensivist (Table E1). References – (67)
<i>Admission injury severity data</i>	
<b>AIS</b>	Abbreviated Injury Scale. Numerical method for comparing injuries by severity, allocated to one of six body regions (head, including cervical spine; face; chest, including thoracic spine; abdomen, including lumbar spine; extremities, including pelvis; and external). It is based on a 6-point ordinal severity scale ranging from AIS 1 (minor) to AIS 6 (maximum). The AIS doesn't assess the combination of multiple-injured patients. The Maximum AIS (MAIS), which is the highest single AIS score in a patient with multiple injuries, has been used to describe overall severity (Table E2). References - (101, 102)
<b>ISS</b>	Injury Severity Score. Anatomical scoring tool that provides an overall score for patients with single system or multiple system injuries. The ISS is the sum of the squares of the highest AIS score in each of the three most severely injured body regions. ISS scores range from 1 to 75, with higher ISS indicating more severe injuries (Table E3). References (103)
<b>RTS</b>	Revised Trauma Score. Physiological index of injury severity, calculated from GCS, systolic blood pressure (SBP) and respiratory rate (RR). These values are multiplied by weights determined by logistic regression of a baseline dataset $S=0.9368(GCS)+0.7326(SBP)+0.2908(RR)$ . RTS takes values between 0 and 7.8408; higher values are associated with improved prognoses. References - (68, 69)
<b>GCS</b>	Glasgow Coma Score. Standardized system for assessing the degree of conscious impairment, involving 3 determinants: eye opening response (E), verbal response (V), motor response (M). M is a 6-point scale varying from 'no response' to 'obeys verbal commands'. V is a 5-point scale varying from 'no response' to 'oriented' and E is a 4-point scale varying from 'none' to 'spontaneous'. GCS can range from 3 (lowest) to 15 (highest) (Table E4). References - (70-72)
<i>Physiologic and laboratory data</i>	
<b>FiO2/PaO2 ratio</b>	Index to characterize the acute respiratory distress syndrome.
<b>IAP</b>	Intra-Abdominal Pressure. Pressure concealed within the abdominal cavity; expressed in mmHg. Normal IAP is ~ 5-7 mmHg in critically ill adults.
<b>IAH</b>	Intra-Abdominal Hypertension. Sustained or repeated pathologic elevation of IAP $\geq$ 12 mmHg. IAH is graded as follows: Grade I: IAP 12-15 mmHg, Grade II: IAP 16-20 mmHg, Grade III: IAP 21-25 mmHg, Grade IV: IAP $>$ 25 mmHg. Reference - (9)

**Table E1**

<u>Sabadell score</u>	<u>Prognosis</u>	<u>ICU readmission</u>
0	Good for >6 months survival	Unrestricted if needed
1	Poor for >6 months survival	Unrestricted if needed
2	Poor for <6 months survival	Debatable
3	Poor for hospital survival	Not recommended

**Table E2**

<u>AIS Code</u>	<u>Description</u>
1	Minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Maximum

**Table E3**

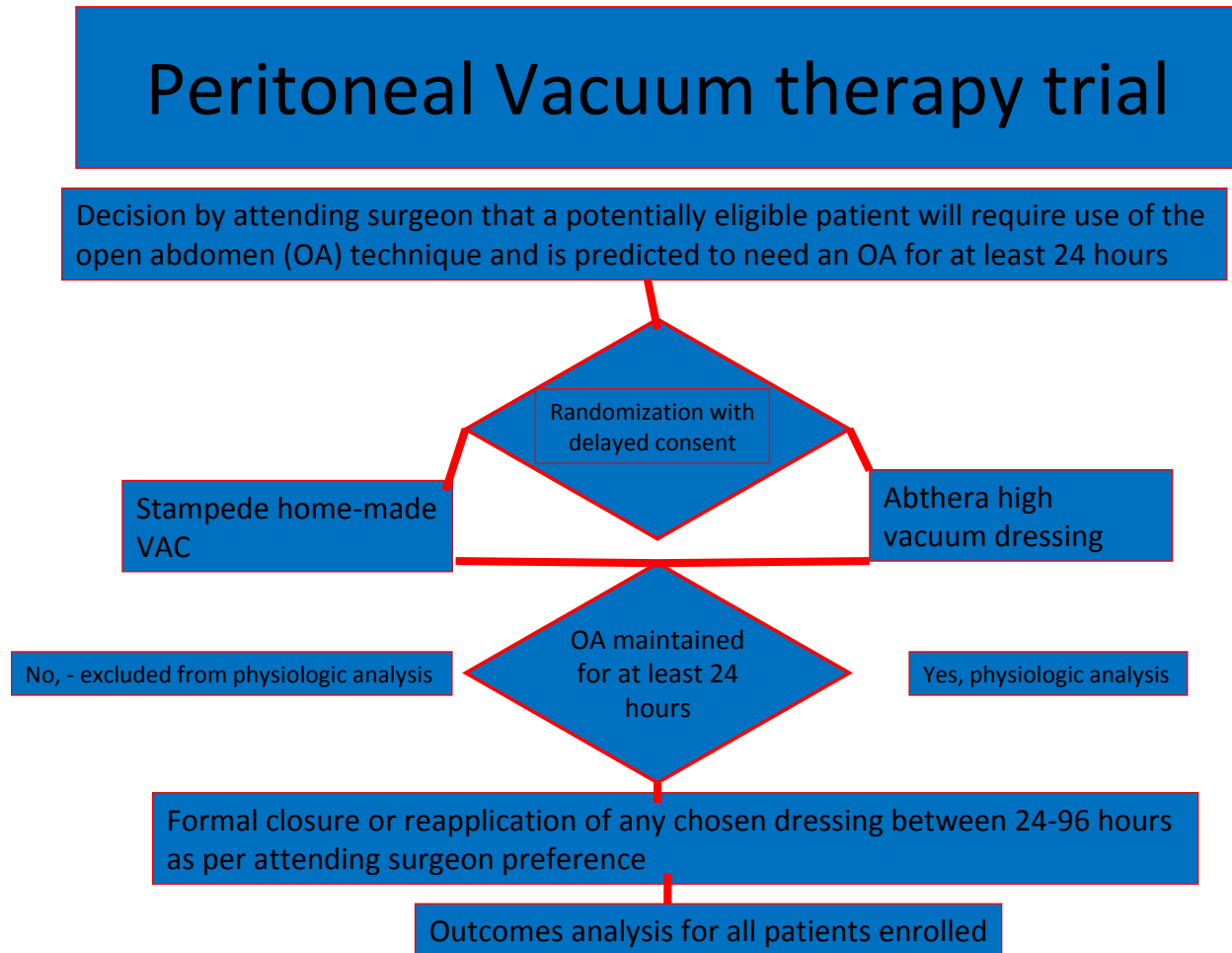
<u>Example of ISS Calculation</u>				
ISS BODY REGION	INJURY	AIS CODE	HIGHEST AIS	AIS <sup>2</sup>
Head/Neck:	Cerebral contusion	140602.3	4	16
	Internal carotid artery, complete transaction	320212.4		
Face:	Ear Laceration	210600.1	1	
Chest:	Rib fractures left side, ribs 3-4	450220.2	2	
Abdomen:	Retroperitoneal hematoma	543800.3	3	9
Extremities:	Fractured femur	851800.3	3	9
External:	Overall abrasions	910200.1	1	
				<b>ISS=34</b>



**Table E4**

<b><u>Total score of the GCS</u></b>		
<b>Eye Opening Response</b>	<b>Motor Response</b>	<b>Verbal Response</b>
Spontaneous=4	Obeys Commands=6	IF NOT INTUBATED:
To Voice=3	Localizes to Pain=5	Oriented=5
To Pain=2	Flexion/Withdrawal=4	Confused=4
None=1	Abnormal Flexion=3	Innapropriate=3
	Extension=2	Incomprehensible=2
	No Response=1	No Response=1
		IF INTUBATED:
		Appears to be able to converse=5
		Ability to converse questionable=3
		Unresponsive=1

**Figure 1 – Flowchart of Study Overview**



**Figure 2. Typical Calgary home-made “Stampede VAC”**



Typical Calgary home-made “Stampede VAC”

**Figure 3. AbThera Commercial VAC in use at Foothills Medical Centre**



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