Draft Study Proposal for Procedures and Protocols

Closed or Open after Source Control Laparotomy for Severe Complicated Intra-Abdominal Sepsis: A randomized controlled clinical trial

Draft 3.0 Dec 017

Clinical Trials Registration at;

https://clinicaltrials.gov/ct2/show/NCT03163095

This Protocol has been written to comply with the Standard Protocol Items: Recommendations for Interventional Trials(1-4) and configured to document the World Health Organization Trial Registration Data Set information(5), and is registered with the National Institutes of Health

World Health Organization Trial Registration Data Set

1. **Primary Register: Clinical Trials Registration at;** https://clinicaltrials.gov/ct2/show/NCT03163095

2. **Date of Registration:**

3. **Secondary identifying numbers:**

    a. **Provincial Research Administration Administrative Approval for Research to Proceed June 19, 2017; REB16-1588**
    b. **Conjoint Health Research Ethics Board (CHREB) Ethics ID: REB16-1588**

4. **Sources of Monetary Support**
    a. **Unrestricted gift from the Acelity Corporation**
    b. **The Snyder Laboratory, University of Calgary**
    c. **Department of Critical Care Medicine, University of Calgary**
5. **Primary Sponsor: World Society of Emergency Surgery**
6. **Secondary Sponsor: The Abdominal Compartment Society**
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9. **Public Title; Closed or Open after Source Control Laparotomy for Severe Complicated Intra-Abdominal Sepsis: A randomized controlled clinical trial**

10. **Closed or Open after Source Control Laparotomy (COOL) for Severe Complicated Intra-Abdominal Sepsis: A randomized controlled clinical trial**

11. **Countries of Recruitment: Canada, Italy, Brazil, Unites States of America, Israel, Ireland, Finland, Australia**

12. **Health Condition Studied: Severe Intra-peritoneal sepsis**

13. **Interventions: Closing the fascia or not after the index source control laparotomy in cases of severe complicated intra-peritoneal sepsis. Not closing the fascia will involve the utilization of a temporary abdominal closure (TAC) device utilizing negative pressure peritoneal pressure (NPPT)**

14. **Inclusion criteria: this study will enroll only those severely ill with intra-peritoneal sepsis. Those patients will be identified by;**

a) Hypotension requiring pressors for MAP > 65 AND
Serum lactate > 2 mmol/litre after resuscitation

<u>OR</u>

b) PIRO 3 or more

<u>OR</u>

c) WSES Score 8 or more

AND

Complicated 2° peritonitis as identified by:

- **(uncontained or unconfined);**
- **Purulence**
- **Feculence**
- **Enteric spillage**

The Exclusion criteria will be;

a) pregnancy

b) confirmed or strongly suspected severe IAH (IAP > 20 mmHg) based on;

i) concerning rise in ventilator pressure assessed by the anesthetist;

ii) increase in IAP measured in the bladder greater than 20 mmHg;

iii) physical inability of the surgical team to close the fascia without "undo pressure";

iv) intra-operatively determined absolute requirement for "Damage Control" surgery including intra-peritoneal packing or non-anatomic post-surgical anatomy (ie surgically placed permanent packing or non-anastomosed bowel ends will not be purposefully closed within intact fascia.

c) there is no intentional of providing ongoing care (ie the treating team wishes to close the abdomen to leave the operating room with the sole intention of withdrawing aggressive measures and providing only "comfort Care" in the ICU.

d) laparoscopic surgery

e) pancreatitis as the source of peritonitis

f) acute superior mesenteric artery occlusion s the primary pathology

g) previous co-enrollment in another investigational study

h) peritoneal carcinomatosis

i) acute presentation with traumatic injury (within 24 hours of injury)

j) age < 18

k) uncontrolled bleeding

15. **Study Type: Variable Block Intra-Operatively Randomized Single Blinded Analysis two treatment arms**
16. **Date of First Enrollment: March 2018**
17. **Target Sample Size: Dynamic Sample Size Calculation Project 320 – 500 patients**
18. **Recruitment Status: Pending**
19. **Primary Outcomes: 90 Day Mortality**
20. **Key Secondary Outcomes:**
    a. **90 day hospital free days**
    b. **90 day ICU free days**
    c. **90 day Ventilator free days**
    d. **90 day renal replacement free days**
21. **Role of the Sponsor(s)**
    a. **The Acelity Corporation (San Antonio, Texas) provided unrestricted funding for am Investigators Planning Meting in Parma, Italy on November 26 2017. The Acelity Corporation had no input into the design of the study and has no control of the analysis, interpretation, or dissemination of the trial data and results all of which remain under the sole control of the Academic Independent Investigators.**
    b. **The Snyder Laboratory from the University of Calgary, will provide direct costs for the conduct of immunological assays including but not restricted to the performance of laboratory studies and the provision of reagents. The analysis, interpretation, or dissemination of the trial data and results of these investigations will remain under the sole control of the Academic Independent Investigators including the Snyder Laboratory.**
    c. **The Department of critical care Medicine from the University of Calgary, will provide unrestricted academic funding to support the conduct of the randomized trial. The analysis, interpretation, or dissemination of the trial data and results of these investigations will remain under the sole**

control of the Academic Independent Investigators including the Department of Critical Care Medicine at the University of Calgary.

Roles and Responsibilities

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Endorsing Scientific Societies

The Abdominal Compartment Society

https://www.wsacs.org

World Society of Emergency Surgery

https://www.wses.org.uk/

Trauma Association of Canada

http://www.traumacanada.org/

Canadian Association of General Surgeons

http://cags-accg.ca/

EXPANDED ABSTRACT

Introduction

Severe complicated intra-abdominal sepsis (SCIAS) is a World-Wide challenge, with high mortality rates, and ever increasing incidence. Mortality rates range from over 10% to 40% when shock is present. According to the WISS study of the World Society of Emergency Surgery (WSES) patients treated for severe peritonitis with a WISS score ≥ 7 experienced a mortality of 41.7%. Most cases result from secondary peritonitis in which there is a physical disruption of the integrity of the gastrointestinal (GI) tract leading to contamination of the peritoneal cavity. Ultimately, however the resultant organ damage that frequently becomes progressive and self-perpetuating results from auto-amplifying biomediator generation and systemic inflammation. The key principles of treating SIAS are early antibiotic administration and the earliest possible operative intervention to provide source control of GI perforations/disruptions. A further potential therapeutic option may be to utilize open abdomen (OA) management with active negative peritoneal pressure therapy (ANPPT) to remove intra-peritoneal inflammatory ascites and to ameliorate the systemic damage from SCIAS. Recent data from a randomized controlled trial including either severe peritonitis or severe trauma, showed as the 30-days mortality is different between commercial open abdomen systems and non-commercial technique with a mean mortality between the two groups of 25-30%.

Although there is now a biologic rationale for such an intervention as well as non-standardized and erratic clinical utilization currently, this remains a novel therapy with potential side effects and much clinical equipoise. Thus, the Closed Or Open after Laparotomy (COOL) study will constitute a prospective controlled randomized trial to address this issue.

Significance:

ANPPT has been highly effective in animal models in reducing the local and systemic damage associated with SCIAS. Survival advantages have also been suggested in both randomized and non-randomized human trials including SCIAS in the inception cohort. However, current guidelines and suggested standard of care recommend not utilizing OA with ANPPT in cases of SCIAS. Thus, high quality data to direct clinical decision making in this highly lethal condition is urgently required, a position espoused by both the Abdominal Compartment Society and the World Society of Emergency Surgery.

Intervention: The study intervention will comprise the randomized decision to either A) primarily close the fascia after laparotomy for SCIAS (CLOSED); or B) leave the fascia open after laparotomy for SCIAS and apply a ANPPT temporary abdominal closure (TAC) device (OPEN).

Study Hypothesis:

ANPPT will reduce the mortality of patients with SCIAS undergoing laparotomy for source control from 42% to 30%, and will reduce the degree of organ dysfunction in association with systemic reduction in Biomediator activation.

The trial will be pragmatic permitting any procedure leaving the fascia open with some formal active negative pressure peritoneal therapy (ANPPT) device versus any that closes the fascia. Thus, allowed techniques for open include are all the commercial OA techniques with or without fascial traction devices. Techniques without ANPPT such as the Barkers VAC PAC, Bagotta Bag, or mesh interposition ***without*** peritoneal suction will not be eligible techniques.

Primary Outcome: 90-Day hospital survival after laparotomy for SCIAS.

Secondary Outcomes: Secondary outcomes will be considered logistical, physiologic, and economic. Logistical outcomes will include Days Free Of (DFO); ICU, ventilation, renal replacement therapy, and hospital at 90 days from the Index Laparotomy. The physiological secondary outcomes will include change in APACHE II, SOFA, RIFLE, ARDS scores after laparotomy. Biomediator outcomes for centres participating in COOL-Max will consist of the measurement of IL-6 and 10, Procalcitonin, Activated Protein C (APC), High-Mobility Group Box Protein 1, and mitochondrial DNA. Economic secondary outcomes will comprise standard costing for utilization of hospital resources.

Inclusion Criteria: Patients will be randomized intra-operatively once it is determined that severe complicated Severe Complicated Intra-Abdominal Sepsis (SCIAS) is present. Severe will be inferred by the presence of septic shock as defined by the Sepsis-3 definition of those requiring vasopressors to maintain mean blood pressure greater than 65 mmHg and having a serum lactate level > 2 mmol/l **OR** Predisposition-Infection-Response-Organ Dysfunction (PIRO) Score of 4 or more **OR** a a positive QuickSOFA (qSOFA) score. qSOFA will be calculated as it is considered as criteria for those likely to have a prolonged ICU stay or die. These simple predictors are; respiratory rate > 22/min; altered mentation; systolic blood pressure < 100 mmHg, AND COMPLICATED due to presence of purulent, feculent, or enteric spillage over at least 2 intra-peritoneal quadrants which can only be identified at laparotomy. Recent studies have confirmed that the simple qSOFA model performs similarly to more complex models like SOFA or LODS outside the ICU.

Exclusion Criteria:

Among those undergoing laparotomy for secondary causes of SCIAS patients will be excluded if; a) pancreatitis, b) they are pregnant, c) physical inability of the surgical team to close the fascia without “undo pressure”; iv) absolute requirement for repeat laparotomy including intra-peritoneal packing or non-anatomic post-surgical anatomy. It should be stated that there is an increasing use of the open abdomen technique after resection with delayed anastomosis for SCIAS, and therefore the screening log of non-eligible patients with this indication will constitute a third important (albeit non-randomized) study group.

Allocation Methodology:

Multicenter prospectively block randomized non-blinded controlled trial. Patients will be identified by the attending trauma surgeons of the participating centers as those undergoing urgent laparotomy for severe sepsis. Randomization will occur intra-operatively with either the preoperative signing of informed consent or under waiver of consent depending on local Ethical Guidelines. Once COMPLICATED peritonitis involving more than 2 quadrants is confirmed eligible patients will be randomized to OPEN or CLOSED through direct online randomization over the internet.

Sample Size: An reasonable estimate was for a 42% mortality closed versus 27% open, given a sample size of 170 per arm, with an power of 80% and an alpha of 0.05. With 15 centres, this would mean about 11 patients per year over 2 years, and with 10 centres, 17 patients per year.

Measurements:
Biomediators and standard hematological and chemical measurements to allow for APACHE II and SOFA scoring (WBC, lactate, ABGs, etc) will be measured every 6 hours for 48 hours, followed by daily for 96 hours, and at the conclusion of the first week.

The trial will be held on a web platform (Clinical Registers) through a dedicated web site: www.clinicalregisters.org (https://www.clinicalregisters.org/).

Anticipated Study Schedule:
The COOL investigators hope to begin enrollment in Jan 2018 and will complete patient accrual by Jan 2020 with initial expedited publication of results in July 2020.
COOL-Max versus **COOL-Lite**: The study will be powered to detect a mortality difference between the 2 allocated therapies (COAST-SSP study). Thus the critical determinant of a potential geographical site being able to participate is ethical approval and willingness to randomly allocate eligible patients to either study protocol. All sites will be requested to obtain serum and peritoneal fluid samples for Biomediator level determination (**COOL-Max**). If a site does not have the laboratory or financial resources however to collect and process study samples for Biomediator analysis they will be eligible to participate without the collection of the Biomediator samples (**COOL-Lite**).
COOL-Mic: will also be considered regarding understanding the microbiology of secondary peritonitis in the OA arm of **COOL-Lite** and to follow the subsequent modifications in microbiologic flora including and patients in the CLOSED arm who require reoperation

Clinical Trials Registration at;

https://clinicaltrials.gov/ct2/show/NCT03163095

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Appendices and Figures

LIST OF AMMENDMENTS

1) Dec 2 2017 Inclusion Criteria Amended

Inclusion Criteria was amended to constitute; a) Hypotension requiring pressors for MAP > 65 (AND) Serum lactate > 2 mmol/litre after resuscitation OR b) a PIRO 4 or more OR c) WSES Score 8 or more; IN ADDITION to Complicated 2° peritonitis (uncontained or unconfined) with Purulence, Feculence, or Enteric spillage.

2) Dec 2 2017 Exclusion Criteria Expanded

The Exclusion Criteria for the study was expanded to include the following list of exclusions;

Patient will need to be excluded from Enrollment and Randomization if;

a) they are pregnant,

b) they have confirmed or strongly suspected severe IAH (IAP > 20 mmHg) based on;

i) concerning rise in ventilator pressure assessed by the anesthetist;

ii) increase in IAP measured in the bladder greater than 20 mmHg;

iii) physical inability of the surgical team to close the fascia without "undo pressure";

iv) intra-operatively determined absolute requirement for "Damage Control" surgery including intra-peritoneal packing or non-anatomic post-surgical anatomy (ie surgically placed permanent packing or non-anastomosed bowel ends will not be purposefully closed within intact fascia.

c) there is no intentional of providing ongoing care (ie the treating team wishes to close the abdomen to leave the operating room with the sole intention of withdrawing aggressive measures and providing only "comfort Care" in the ICU.

d) laparoscopic surgery (no open laparotomy)

e) pancreatitis as the source of peritonitis

f) acute superior mesenteric artery occlusion

g) no co-enrollment in another investigational study

h) carcinomatosis

i) acute presentation with traumatic injury (within 24 hours of injury)

j) age < 18

k) uncontrolled bleeding

Introduction

Sepsis is a global health problem that has defied all the technical advances of our time to become an ever-increasing cause of death through-out the world(6). International consensus has concurred that sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. In the most severe cases mortality rates approach 30-40%, and there are an ever-increasing estimated number of cases per year approaching 18 million worldwide per year(7-10). When the focus of infection is located within the abdominal cavity, a particularly severe form of sepsis may result in association with the particular anatomic and physiologic characteristics of the abdominal cavity and the viscera within.

Intra-abdominal sepsis (SCIAS) thus remains the 2nd most common cause of sepsis. The most recent Sepsis-3 Consensus Definitions from the Society of Critical Care Medicine and the European Society of Intensive Care Medicine (11). These newest guidelines, which consider the importance of the pathobiology of sepsis), emphasize the life-threatening nature of organ dysfunction with the view that cellular defects underlie physiological and biochemical abnormalities within specific organ systems. Under this terminology "severe sepsis" becomes superfluous(11, 12). While greatly respecting this concept, surgeons making intra-operative decisions require practical decision making tools, and thus the concepts of severe espoused by the World Society of Emergency Surgery will be retained although interpreted within the newer Sepsis-3 Framework. From a functional clinical perspective, cases have been defined as severe when sepsis is associated with observed organ dysfunction(13-16).

Cases are also defined as complicated when the inflammation or contamination spreads beyond a single organ, causing either localized or diffuse peritonitis(13, 17). SCIAS requires aggressive surgical intervention requiring large inputs of resources from different hospital departments and disciplines. SCAIS typically resulting from secondary peritonitis may be distinguished from other causes of severe sepsis through a requirement for surgical abdominal exploration to surgically address the breech in the gastrointestinal (GI) tract. However, despite advances in diagnosis, surgery, and antimicrobial therapy, mortality rates associated with complicated intra-abdominal infections and intra-abdominal sepsis remain exceedingly high(16). Currently one third or more of patients afflicted with severe non-traumatic intra-peritoneal sepsis will succumb to this disease(18). As recommended by the World Society of Emergency Surgery (WSES), patients with severe sepsis or septic shock of abdominal origin require early hemodynamic support, source control, and antimicrobial therapy(17). Despite such practical recommendations however, SIAS may result in progression to septic shock and multiple organ dysfunction ultimately driven by excessive inflammation. There is great variability in the human immune response to an infectious focus, and some individuals will greatly over-react to an inciting infection with a massive Biomediator storm that propagates multi-system organ failure and death whereas other individuals have little or no response to the same stimuli. Alternatively, the failure to obtain adequate source control of the cause of SIAS has been identified as an independent predictor of mortality in SIAS(19). However, recognizing “failed source control”(20, 21), from a selfpropagating Biomediator storm is often difficult or impossible without abdominal re-exploration (relaparotomy).

Given the severity of SCIAS with poor outcomes often controversial surgical therapies have been debated. Despite, the appeal of a single therapeutic "cure, relaparotomy may frequently be necessary to eliminate persistent peritonitis or new infectious foci(22-24). In those randomized to expectant management AFTER laparotomy for intra-abdominal sepsis, 42% still required relaparotomy for suspected or proven persistent peritonitis in a large Dutch multi-centre trial(22). Until recently, two debated surgical approaches to ensuring source control in the peritoneal cavity consisted of "laparotomy on demand – (LOD)" versus "planned re-laparotomy" (PRL)(22, 25, 26). In a planned re-laparotomy strategy, re-laparotomy was routinely performed every 36-48 hours in order to inspect, drain, and lavage the abdominal cavity until the intra-operative findings were negative for peritonitis(22). Re-laparotomy on demand offers repeat laparotomy only in those patients in whom the lack of clinical improvement or even clinical deterioration has suggested that on-going peritonitis has resulted from either persistent peritonitis or a new infectious focus(22). The relative merits of either approach have been widely debated for many years, but were best addressed by the large RCT conducted by Van Ruler et al(22)., which noted no difference in mortality between the two approaches, although the ROL strategy reduced direct medical costs by 23%(22). The equivalence in outcomes, coupled with an apparent cost-savings, has generated Consensus Guidelines that recommended that LOD after laparotomy for peritonitis be adopted as the standard of care(27). Upon critical review the mortality in this RCT of severe secondary peritonitis well illustrates the devastating nature of this disease with the resultant mortality of approximately 1/3 of all afflicted patients. No matter which cohort is considered, such a dismal outcome demands alternate approaches to attempt to save more lives.

At present, pharmacologic approaches are not the answer. Despite the continuous general improvement in supportive critical care that has occurred over time, there has not been any seminal advances in addressing the central dysregulated inflammation that ultimately causes the organ damage that kills or maims patients with severe sepsis. Attempting to derive pharmacologic therapies for combating post-infective inflammation has proved to be an incredibly expensive and frustrating process so far. There have been literally 100's of failed anti-mediator trials and thus the developmental pipeline for novel therapeutics to treat sepsis has diminished to a trickle with repeated failures and even the one potential drug APC, being taken off the market(28). Over one hundred attempts at blocking single biological response mediators have failed examining the early cytokine storm of sepsis(29). It has become readily apparent from these failed anti-mediator trials, that attempt to neutralize, block, or promote a single biomediator(s) after they have been generated is not currently helpful(29).

Secondary peritonitis ultimately remains a surgical disease. Thus it appears that the only potential options to improve outcomes in SCIAS, are surgical in nature. A controversial, potentially morbid, potentially life-saving technique in surgery is the adoption of a Damage control approach to surgery especially when conducting laparotomy. The rationale and conduct of Damage Control derives from abbreviated, expedited surgical approaches used in trauma, aiming to arrest hemorrhage, and to control enteric and other biological fluid contamination, using non-definitive, often non-anatomic techniques that require a follow-up operation to complete(30-32). One of the most common Damage-control techniques utilized is not closing the mid-line fascia post-operatively, which be definition constitutes an open abdomen technique(27, 33). The focused aim is to arrest the physiologic insult of severe trauma which most often includes hemorrhage and resultant progressive ischemia. Although not typically due to hemorrhage, SCIAS also induces progressive ischemia and tissue damage that must be reversed as soon as possible for patient survival. Ultimately this organ dysfunction is associated with a progressive oxygen deficit, ongoing organ failure, massive biomediator generation, in a progressive downward spiral. Non-trauma Damage Control surgery thus attempts to break this downward spiral, through emergent surgical intervention, aimed at controlling enteric leakage, removal of ischemic tissue, without regard to completing the formal laparotomy. It is increasingly being reported in uncontrolled series, as another potentially desirable option for the sickest SCIAS patents(13, 20, 21, 34-36).

Use of the OA in severe sepsis may thus allow early identification and increased drainage of any residual infection, control any persistent source of infection, more effectively remove biomediator rich peritoneal fluid, prophylaxis against the abdominal compartment syndrome, and allow for the safe deferral of gastrointestinal re-anastomosis(13). Compared to trauma patients however, patients undergoing OA management for intra-abdominal sepsis have greater risks subsequent to OA utilization, including entero-atmospheric fistula (EAF), intra-abdominal abscesses, and lower rates of definitive fascial closure(13, 15, 37). Non-trauma patients especially with peritonitis seem to be more prone than trauma patients to develop complications of the OA(38, 39), especially the feared entero-atmospheric fistula (EAF)(39, 40).

Although, case series reporting the use of an OA strategy after non-trauma laparotomies have been reported there are no other contemporary randomized studies to address this critical issue. There has only been one other RCT conducted prior to 2006 that randomized patients to a closed or open strategy, but the techniques of OA management used were inadequate by today's standards noting that the management of an OA has undergone dramatic improvements I technology and technique in recent years. Robledo and colleagues randomized patients severe secondary peritonitis to open or closed strategies after laparotomy, using a non-absorbable polypropylene (Marlex) mesh in a interposed position between the open fascia, thus exposing the underlying bowel to great risk of enterocutaneous fistula(41). The study was stopped at the first interim analysis. Although the mortality differences between the two groups did not reach statistical significance, the relative risks and odds ratio for death were higher with an OA strategy(41). The OA Management technique used in this study(41) would appear to be clearly inadequate by today's standards. Although RCT data comparing techniques is badly needed, meta-analyses conducted by both ourselves(42) and the Amsterdam group(38) (Dr M BoerMeester – Steering Committee Member) have concluded that NPWT treatment appears to be both safest and most effective open abdomen management technique currently available. The commercial NPPT therapy systems now available for OA have greatly reduced the risks of enterocutaneous fistula, and thus greatly increased the safety for the patient.

A more fundamental attribute to consider offering an OA is the fact that OA with newer active NPPT may facilitates the delivery of a new novel therapy to the peritoneal cavity; that of active Negative Peritoneal Pressure therapy (NPPT)(27, 42, 43). Both animal(44) and in-silica modeling of these animal studies(45) have shown reduced plasma Biomediator levels with enhanced NPPT in a randomized trial comparing NPPT to passive peritoneal drainage. Systemic inflammation (TNF-α, IL-1β, IL-6) was significantly reduced in the NPPT group and was associated with significant improvement in intestine, lung, kidney, and liver histopathology(44). Although the mortality rate in the NPPT was 17% versus 50% in the control group, but this difference was not statistically significant (P = 0.1859) likely due to the smaller numbers. A larger prospective but non-randomized multi-centre cohort study in critically ill/injured patients requiring an open abdomen, enrolled 280 patients from 20 sites, in whom 168 underwent at least 48 hours of consistent OA therapy(46). The two types of OA therapy possible were enhanced or standard NPPT. Although Biomediator levels were not measured in this trial, the 30 day all-cause mortality rate was 14% in those treated with NPPT and 50% in those with the passive therapy and the OA(46).

Our research group has conducted the only prospective randomized controlled trial addressing this question; the Peritoneal VAC trial(47). This RCT, conducted in Calgary, enrolled 45 out of 63 potentially eligible patients over a 15 month period between Sept 2011 and Dec 2012. Patients were enrolled in the operating room after an attending surgeon made the critical decision that an abbreviated laparotomy was required in critically ill/injured patients. In additional to numerous physiological variables, Biomediator levels were measured every 24 hours in the initial post-laparotomy phase of critical care(47, 48). Although standard Biomediator levels were not statistically different nor was peritoneal fluid drainage, the 90-day mortality rate was improved in the active NPPT group (hazard ratio, 0.32; 95% confidence interval, 0.11–0.93; P=0.04)(47). A valid critique of the Peritoneal VAC trial was that despite the fact that all patients were deemed to need OA therapy by the attending surgeon, there was still a heterogeneous mix of patients including trauma and non-trauma (although the only statistically significant difference in baseline criteria was more chronic disease in the ANPPT patients)(47). Thus, although unexplained, significantly improved survival with ANPPT does warrant further exploration as a means of breaking the progression to wards MSOF and death in cases of severe SCIAS. The COOL Investigators thus feel that the potential life-saving potential of ANNPT after laparotomy for SCIAS coupled with global clinical equipoise warrants a carefully conducted randomized prospective study.

The Peritoneal Cavity as a Reservoir for Systemic Inflammation

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(49-51). Although extremely complicated, visceral ischemia further characteristically generates multiple immunological mediators with the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α), and interleukin six (IL-6), as well as inhibitive cytokines such as interleukin ten (IL-10)(52-55). Post-operative complications associate with increasing levels of systemic IL-6, and peritoneal TNF- α(54, 56). 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(57). Overall, the peritoneal cytokine response is much higher than the systemic response in peritonitis(55, 58-60). In a series of rat studies, Hendriks and colleagues demonstrated that peritoneal cytokine levels (especially IL-6, TNF- α, (61)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(58). 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(62-65).

We believe that if it can be done safely, it is logical to attempt to remove intra-peritoneal Biomediators to potentially ameliorate the local effects and to prevent their being absorbed systematically. 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(66, 67), more structured studies could not confirm such benefits(68-70). 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(71-73). 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(65).

ANNPT therapy may be a more direct and focused solution to this complicated problem, and one that will be complementary to the other benefits of OA use in the sickest patients. 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 a stated secondary but important objective of the COOL-MAX arm of this trial.

Another potential benefit of ANPTT after severe infection may be the attendant decompression of the abdominal compartment and prevention of even modest degrees of IAH. Patients with intra-abdominal infections are at risk of elevated IAP both as a result of the primary intra-peritoneal disease, as any large fluid resuscitation often required to maintain organ perfusion(74-76). 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(77, 78). 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(79). 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(80). Although direct translation to humans is uncertain, even modest degrees of IAH (often clinically ignored) have been found to have profound far reaching effects on propagating multiple organ failure in animals with ischemia/intra-peritoneal infections(81-83).

This proposed study will thus address critical issues concerning a disease process that currently kills more than one-third of those afflicted, answering an urgent need for randomized controlled trial raised by other authors after reviewing this problem(34, 84).

ORPHAN TEXT

It is hard to know what “severe’ contamination means in reality. It is hard to compare one surgeons severe to another’s. Some studies have reported terminating the repeated laparotomy cycle when the peritoneal cavity was “macroscopically clean”(85), but how to judge this remains currently impractical and poorly defined.

It has been reported that peritoneal washing is immunosuppressive(85).

Intervention

Patients will be randomized intra-operatively once it is determined that complicated SCIAS is present. SIAS will be defined and denoted by the presence of **SEVERE** due to the presence of any organ dysfunction or identification by the qSOFA score AND **COMPLICATED** due to presence of purulent, feculent, or enteric spillage over at least 2 intra-peritoneal quadrants.

Once this eligibility is confirmed they will be randomized to either;

ROD) - Re-Laparotomy on Demand – primary closure of the fascia with placement of an intra-peritoneal drain (such as a Jackson-Pratt drain)

OR

OA-aNNPT) – Open Abdomen with active Negative Pressure Peritoneal Therapy – the fascia will not be closed, and a commercial VAC device will be utilized inside the peritoneal cavity.

Primary Closure and ROD) - Re-Laparotomy on Demand

This strategy will consist of primary closure of the fascia with placement of an intra-peritoneal drain (such as a Jackson-Pratt drain) to allow drainage of intra-peritoneal fluid for both clinical reasons and to facilitate intra-peritoneal fluid testing. Closure or not of the skin will be left to the attending surgeons discretion. There will be no formal requirement for relaparotomy. Post-operative diagnostic imaging, and all other aspects of post-operative care shall be at the discretion of the treating critical care/surgical teams. Any decision to perform a relaparotomy will be at the discretion of the treating critical care/surgical teams, and in no way mandated by this study, although this will constitute a study outcome. If at any subsequent laparotomy the attending and responsible surgeon selects an open abdominal strategy as being in the patients best interest this will be permitted and the outcomes will be analyzed considering the original intention to treat allocation at enrollment. Any application of any wound suction or negative pressure device to the soft tissue above the fascia will be permitted but will not change the understanding that the fascia has been formally closed and this is a CLOSED abdominal patient.

OA-ANNPT) – Open Abdomen with active Negative Pressure Peritoneal Therapy

The time that the TAC 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 24-72 hours from placement at the Foothills Medical Centre. This is congruent with International Guidelines for TAC changes, although it is understood there is little scientific evidence guiding these practices(13, 17, 86). The primary outcome of mortality will analyzed based on the initial allocated study arm regardless of the duration of TAC application, however, secondary outcomes involving Biomediator outcomes and intra-peritoneal drainage will be assessed on a Per-Protocol basis

Inclusion Criteria

Inclusion criteria: this study will enroll only those most severely ill with intra-peritoneal sepsis who have septic shock on the basis of intra-peritoneal sepsis. Those patients will be identified by;

Septic Shock or Sepsis with adverse prognosticators identified by;

a) **Hypotension requiring pressors for MAP > 65 (AND) Serum lactate > 2 mmol/litre after resuscitation**

   OR

b) **Predisposition-Infection/Injury-Response-Organ Dysfunction (PIRO) Score 4 or more(87)**

   OR

c) **World Society of Emergency Surgery Sepsis Severity Score 8 or more(14-16)**

IN ADDITION TO

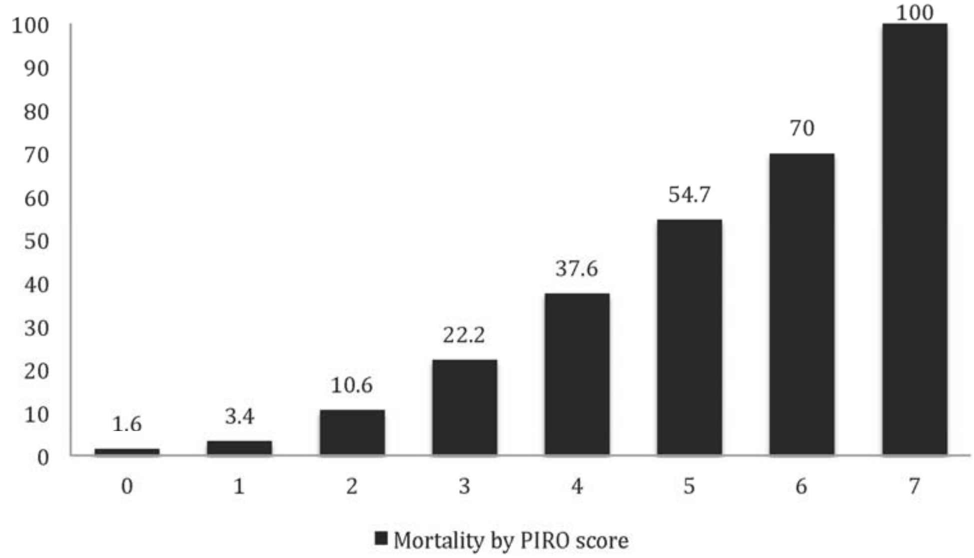
- **Complicated 2° peritonitis (uncontained or unconfined) with Purulence, Feculence, or Enteric spillage.**

Rationale for Inclusion criteria

The combination of hypotension requiring vasopressor therapy and serum lactate greater than 2 mmol/l was found to have the best performance out of a number of different combinations of variables and either indicator alone when extensively review by the Guidelines Task force who crate the new revised Third Consensus Definitions for Sepsis and Septic Shock. This combination of variables demonstrated a 42.3% mortality when evaluated using the Surviving Sepsis Guidelines(11, 12). These indicators will thus reliable indicate patients in septic shock who are at a high risk of death. It is relevant to note that vasopressor dependent hypotension equates to a cardiovascular SOFA component score of ≥ 2(88, 89). It is also pertinent that the new defined lactate threshold of 2 mmol/litre was found to perform as well as earlier cutoffs that were higher in identifying those at a high risk of death, recognizing the serum lactate is a proxy for cellular metabolic abnormality(12).

The predisposition, infection, response and organ dysfunction (PIRO) staging system was designed as a stratification tool to deal with the inherent heterogeneity of septic patients(90). The concept of the predisposition, infection, response, and organ dysfunction (PIRO) scoring system was recommended at the 2001 International Sepsis Definitions Conference to improve the traditional classification of sepsis(91, 92). The PIRO system is an ideal staging system that incorporates assessment of premorbid baseline susceptibility (predisposition), the specific disorder responsible for illness (infection), the response of the host to infection, and the resulting degree of organ dysfunction. The four components of the PIRO system cover multiple known independent factors that may influence the onset, development, and outcome of sepsis(90). PIRO scores have been developed in patients with severe sepsis (93), community acquired pneumonia (CAP) (94) and ventilator associated pneumonia (VAP) (95). They were recently evaluated in a population of septic patients (25% intra-abdominal sepsis) seen in the emergency department and the PIRO score had a significant improved area under the curve than both the APACEHE II and MEDS score(90). Most recently, a specific intra-abdominal sepsis PIRO score has been created in Calgary(87). In this population the PIRO score showed consistent mortality discrimination outperforming both APACHE II and SOFA(87). The mortality rate by PIRO score was 37.6% for a PIRO of 4 and 54.7% for a PIRO of 5. Thus, patients will be recruited into the COOL study if they have a PIRO score of four or more. Use of the PIRO Score is Fully Described in **Appendix ZZZ**

Figure 1. Mortality rate by PIRO score



The final criteria that may be used to identify patients with intra-abdominal sepsis at a high risk of death is a World Society of Emergency Surgery Sepsis Severity Score of 8 points or more, which also indicates a high risk of death. The World Society of Emergency Surgery (WSES) firest derived a Sepsis Severity Score derived from data and experience obtained from a global prospective observational study (CIAOW Study)(15, 96). To derive this score, risk factors for death during hospitalization were evaluated and review by an expert international panel. The most significant variables, adjusted to clinical criteria, were used to create a severity score for patients with Complicated Intra-abdominal infections (cIAIs) including clinical conditions at admission (severe sepsis/septic shock), the origin of the cIAIs, the delay in source control, the setting of acquisition and any risk factors such as age and immunosuppression.

Table 5 WSES sepsis severity score for patients with complicated Intra-abdominal infections (Range: 0–18)

Clinical condition at the admission	
• Severe sepsis (acute organ dysfunction) at the admission	3 score
• Septic shock (acute circulatory failure characterized by persistent arterial hypotension. It always requires vasopressor agents) at the admission	5 score
Setting of acquisition	
• Healthcare associated infection	2 score
Origin of the IAIs	
• Colonic non-diverticular perforation peritonitis	2 score
• Small bowel perforation peritonitis	3 score
• Diverticular diffuse peritonitis	2 score
• Post-operative diffuse peritonitis	2 score
Delay in source control	
• Delayed initial intervention [Preoperative duration of peritonitis (localized or diffuse) > 24 h)]	3 score
Risk factors	
• Age>70	2 score
• Immunosuppression (chronic glucocorticoids, immunosuppresant agents, chemotherapy, lymphatic diseases, virus)	3 score

This predictive system carries the advantage of having been derived in one population of critically ill septic patients and validated in another world-wide population, giving great generalizability to the scoring system. In general, a score above 5.5 was the best predictor of mortality, but scores of 8 or more had a 41.7% mortality(14), very comparable to other groups of patients presenting with septic shock.

Exclusion Criteria

Patient will need to be excluded from Enrollment and Randomization if;

a) they are pregnant,

b) they have confirmed or strongly suspected severe IAH (IAP > 20 mmHg) based on;

i) concerning rise in ventilator pressure assessed by the anesthetist;

ii) increase in IAP measured in the bladder greater than 20 mmHg;

iii) physical inability of the surgical team to close the fascia without "undo pressure";

iv) intra-operatively determined absolute requirement for "Damage Control" surgery including intra-peritoneal packing or non-anatomic post-surgical anatomy (ie surgically placed permanent packing or non-anastomosed bowel ends will not be purposefully closed within intact fascia.

c) there is no intentional of providing ongoing care (ie the treating team wishes to close the abdomen to leave the operating room with the sole intention of withdrawing aggressive measures and providing only "comfort Care" in the ICU.

d) laparoscopic surgery

e) pancreatitis as the source of peritonitis

f) acute superior mesenteric artery occlusion

g) no co-enrollment in another investigational study

h) carcinomatosis

i) acute presentation with traumatic injury (within 24 hours of injury)

j) age < 18

k) uncontrolled bleeding

Study Recruitment Log and Non-Randomized Patients

In current world-wide clinical practice, it is likely that the most common reason for non-eligibility will be the surgeon-based decision to resect a hollow viscus and due to the perceived critical nature of the patient decide not to re-anastomose the bowel but to instead perform Damage Control and return the bowel ends into the peritoneal cavity without a diverting stoma. As this is an absolute indication for a future re-operation these patients will be ineligible for randomization. Although some influential authors are highly critical of this practice [81], others recognize or even recommend this approach(20, 34, 84, 86, 97, 98) .

Biomediator Measurements

Summarized Biomediator Samples for COOL-MAX centres

- Will be drawn from both the serum and peritoneal fluid

Timings

- Enrollment in the OR
- 6 hours post enrollment
- 12 hours post enrollment
- 18 hours post enrollment
- 24 hours post enrollment
- 36 hours post enrollment
- 48 hours post enrollment
- 72 hours post enrollment
- 168 hours (7 days) post enrollment
- 336 hours (14 days) post enrollment
- 720 (30 days) 18 hours post enrollment

After enrollment is confirmed blood will be drawn from an existing arterial or venous line in the OR (being designated the "enrollment sample"). Thereafter the same quantity of blood will be drawn every six hours for the first 48 hours, again at 72 hours, and then weekly until 30 days post enrollment. Fifty (50) ml of peritoneal fluid will also be collected from the abdomen at the same time as serum samples are obtained while the abdomen is either open or while an intra-peritoneal drain is present. Blood samples will be taken from existing vascular catheters and all fluids will essentially be "waste" fluids that would be discarded normally, so there will be of absolutely no discomfort or inconvenience to the patient.

Study Hypothesis

The Null hypothesis will be that there will be no difference in mortality when an Open Abdomen Management Strategy administering active negative pressure peritoneal therapy is utilized compared to a primary fascial closure strategy in patients suffering severe intra-peritoneal sepsis.

Study Setting

The study will be conducted in operating rooms around the world where critically ill patients with severe complicated intra-abdominal sepsis undergo source control laparotomies. The lead study Centre will be the Foothills Medical Centre, a Quaternary Care academic Medical Centre in Alberta, Canada serving a referral base of approximately 2 million people. Potential patients will be identified in the emergency departments, in-patients wards, and critical care units of this Academic referral Centre, but the true eligibility will only be confirmed in the operating room during the conduct and near completion of laparotomy. Other recruiting sites will be world-wide and will include academic centers as well as community hospitals willing to provide full clinical follow-up. A list of supporting centers can be found in **Appendix XXX**

Site Eligibility

Interventions

For those randomized to **CLOSED**, the fascia will be closed at the index source control laparotomy. CLOSED is defined as the primary approximation of the fascia using whatever suture desired in either interrupted or continuous fashion. There is no stipulation on any necessity to actually close the skin, or on whether a skin suction device is utilized, all of which will be at the discretion of the treating clinical team. There will be no prohibition preventing the treating clinical team from re-opening (Re-opening on Demand), if the patients best interest is deemed to be served by re-laparotomy, although this decision will constitute a study outcome.

For those randomized to **OPEN**, the fascia will NOT be closed and an AbThera temporary abdominal closure device will be placed following Manufacturer's directions and/or Institutional protocols. Participating Institutions will be expected to be familiar with the proper utilization of the AbThera device, or else undergo an in-service with a content matter expert on AbThera utilization prior to site participation. The addition of any other fascial tension device such as mesh-mediated fascial closure(99-102), or other fascial tension devices(103) will be permitted as long as an AbThera device is utilized within an abdominal cavity without fascial closure. There will be no requirement or stipulation on how long the abdomen must be left open for in the OPEN arm, other than good practice recommendations recommend attempts to close the abdomen as soon as safely possible(27), and ideally within the first one to two weeks of hospitalization(104, 105).

For both arms of the trial it will be expected that Attending surgeons are involved in either the direct supervision and/or inter-operative participation with either facial closure or temporary abdominal closure in order to be an acceptable participating Centre.

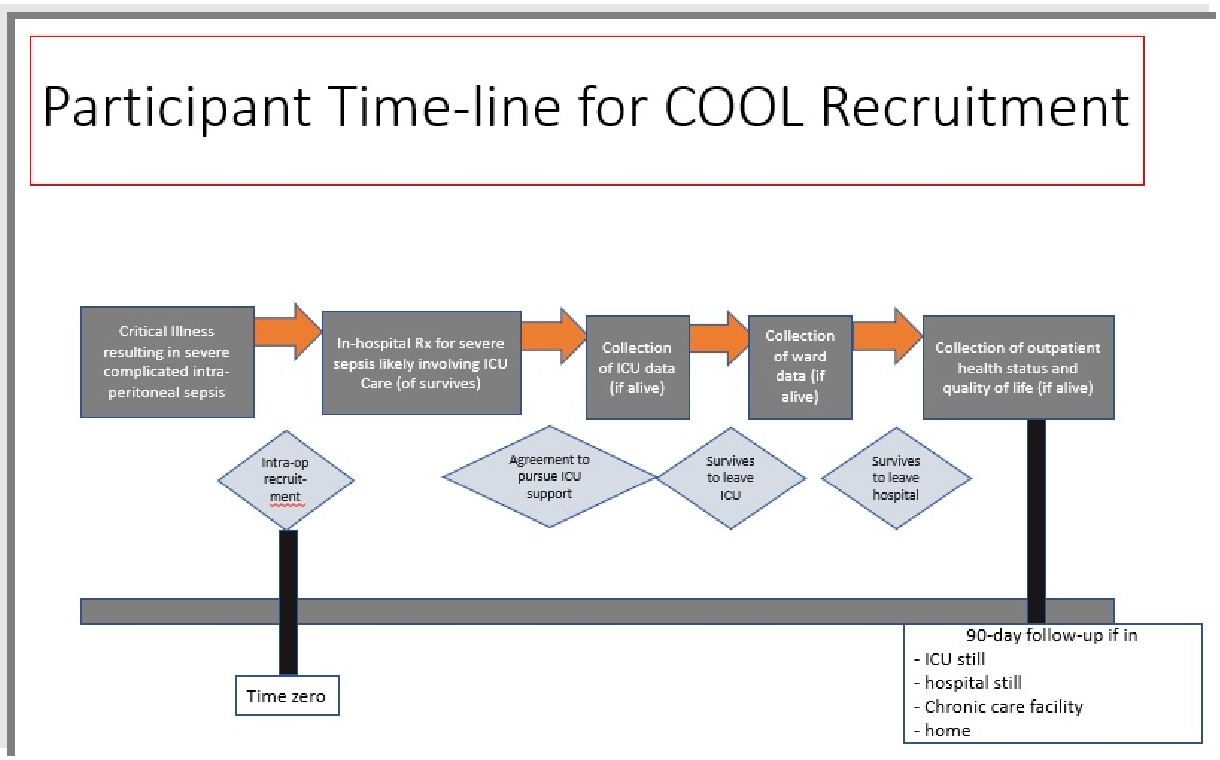
Concomitant Care

Other than the randomly allocated decision to either primary close or leave the abdomen open after source control laparotomy, there will be no mandated or enforced supportive care requirements for on-going clinical care of enrolled patients enrolled in the COOL trial recognizing the many and multiple controversial aspects of critical care support. It will therefore be assumed that the random nature of patient allocation will ensure patients are provided equivalent post-surgical care in either arm.

Primary Outcome Measure

The primary outcome will be death which will be measured using Cox proportional hazards models were used to calculate hazard ratios (HRs) for mortality.

Participant Time-line



Participants will be recruited in the operating room when it is determined that they have complicated intra-peritoneal contamination in addition to severe sepsis. This will be time zero for study recruitment. For those centers participating in COOL-MAX involving the collection of serum and peritoneal fluid samples may potentially be collected at 6, 12, 18, 24, 36, 48, 72, 168, 336, and 720 days after enrollment. A potential economic analysis of al the costs involved in treating severe intra-abdominal sepsis may also collect resource-utilization data on each enrolled patient but no direct patient contact will be required for this other than a one-time ascertainment of ethical permission to access health care administrative data-bases for their costing data.

Sample Size Calculations

The peritoneal VAC study revealed an Intention-to-treat 90-day mortality of 21.7% in the ABThera group versus 50.0% in the Barker's vacuum pack group [HR, 0.32; 95% confidence interval (CI), 0.11– 0.93; P = 0.04]. This 30% reduction in mortality is likely too dramatic to expect to be practically replicated and thus a more conservative effective of 10% reduction in mortality would be appropriate. Thus, given a mortality rate of 33% in the general population of those with severe intra-abdominal sepsis N = 170/arm.

Intention to Treat

The analysis of the primary outcome, mortality will be on an intention to treat basis related to the allocation of initial intra-operative therapy.

Planned Sub-Group Analysis

There will be a planned subgroup analysis of the actuarial mortality stratifying patients into those with and without the presence of septic shock during the first 48 hours after onset of peritonitis (if known and 24 hours before and 24 hours after 1st laparotomy if not known)

Secondary Outcomes

Per-Protocol Biomediator Profile Outcomes

Analysis of Biomediator Profile Kinetics/Dynamics will be on a "per-protocol basis" with per-protocol considered the delivery of at least 24 continuous hours of ANNPT for those randomized to OPEN and at least 24 hours in the first 48 hours post enrolment of fascial closure in those randomized to CLOSED. In addition for those patients recruited in Calgary (and potentially other geographically close sites in Alberta) mass cytometry specimens will be collected from the peritoneal fluid when possible. Mass cytometry is a mass spectrometry technique based on inductively coupled plasma mass spectrometry and time of flight mass spectrometry used for the determination of the properties of cells (cytometry). In this approach, antibodies are conjugated with isotopically pure elements, and these antibodies are used to label cellular proteins. Cells are nebulized and sent through an argon plasma, which ionizes the metal-conjugated antibodies. The metal signals are then analyzed by a time-of-flight mass spectrometer. The approach overcomes limitations of spectral overlap in flow cytometry by utilizing discrete isotopes as a reporter system instead of traditional fluorophores which have broad emission spectra

i) Systemic inflammatory marker levels (e.g. TNF-α, IL-1β, IL-6, IL-10)

ii) Peritoneal fluid inflammatory marker levels (e.g. TNF-α, IL-1β, IL-6, IL-10)

iii) Determination of the type and activation status of inflammatory cells present in the peritoneal fluid.

iv) Measurement of the activation potential of peritoneal fluid CyToff (Mass Cytometry)

v) Peritoneal fluid drainage volume

vi) Post-operative fluid balance

v) a) Mean 24 hour intra-abdominal pressure (IAP)

v) b) daily WSACS IAH grading classification

Intention to Treat Physiological Outcomes

vi) SOFA score and individual organ system components of the score

vii) PaO_2/FiO_2 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

Intention to Treat Global Secondary Outcomes

i) Days with fascial closure for the month after admission

ii) Ventilator free days for the month after admission

iii) ICU free days from the month after admission

iv) Hospital free days from the month after admission

v) 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(106), and a modification of the Charlson Comorbidity Index(107, 108).

2) **Admission illness severity data:** APACHE 2, SOFA(11, 88), Quick-SOFA(11), and Manheim Peritonitis Score(109, 110)

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

Recruitment Strategies

Academic Medical Centers will be recruited primarily from the partner Academic Institutions of the World Society of Emergency Surgery, Abdominal Compartment Society, Canadian Association of General Surgeons, and the Trauma Association of Canada. All these Societies are endorsing the trial, and the institutions involved with these Societies have a history and track record of successful research into intra-abdominal sepsis and open abdomen management research(13, 14, 18, 47, 111-119) as well as fair, equitable, and practical Ethical oversight from their associated institutions. These institutions will be contacted through direct communications between the PI and site investigators, which has actually been an ongoing process recognizing that many renowned and established intra-abdominal sepsis researchers have attended the Protocol Refinement Meeting in Parma, Italy, November 26 2017(120).

In addition to the word of mouth, society communications, and direct emails, the study will also be publicized through the formal academic publication of an concise study protocol document jointly published in the world Journal of Emergency Surgery and the Trauma Surgery & Acute Care Open Journals to increase the dissemination of interest. Finally, many academic presentations will be given by the academic investigators around the world and any interested institutions that are able to fulfill the requirements listed below will be invited to participate in this trial.

Site Eligibility and Infra-Structure Required for Participation

In order for a Hospital or health care system to participate in the COOL study the following resources must be available to the investigators

Minimal System Resources Required for Site Participation in COOL-LITE

- **Designated Primary Investigator** presumably with an Academic Affiliation willing to take overall medical/ethical/academic responsibility for the conduct of the study
- **Ethical Approval –** by the appropriate local ethics committee with oversight of the participating Institution
- **Site Investigators/willing local surgeons** with the responsibility of caring for those with SIAS and thus the ability to recruit patients
- **Internet Access –** either within or closely available to the operating theatre to allow on-line randomization of patients during laparotomy
- **AbThera Dressing Availability** for those randomized to OPEN
- Familiarity with the application of the AbThera Temporary Abdominal Closure (TAC) device – or – willingness to undergo training and in-service on the safe utilization of the AbThera TAC
- **Study Personnel/Investigator** capable to record and compile case record and submit to the Central Study Registry

Full System Resources Required for Site Participation in COOL-MAX

- Above and also;
- Study Personnel capable of obtaining blood/IPF samples
- Laboratory capability to store frozen blood/IPF fluid till study completion and send to Calgary for analysis

Recruitment Issues

Lead Hospital: Foothills Medical (FMC) Centre

The FMC is one of the largest single site hospitals in Canada. It is one of Canada's most recognized medical facilities as well as one of the leading hospitals in Canada, providing advanced healthcare services to over two million people from Calgary, North Western United States, Southern Alberta, southeastern British Columbia and southern Saskatchewan(121). At the FMC acutely ill emergency surgical patients are cared for by the Acute General Surgery Service, attended by staff surgeons on a weekly basis. Patients requiring laparotomy for source control will be taken to the operating room under the care of the Surgical attending who will be present for the operation. It will be the Attending surgeons role to recognize the patients eligibility for the study and to initiate the recruitment process which can all be completed on-line. After care in the ICU is conducted in a closed multi-disciplinary ICU during which time the care is under the direct care of the ICU attending with regular consultative care from the surgeon. The local investigators include both surgeons, and intensivist, as well as dually cross appointed surgical-intensivists. This group was extremely supportive of a similar recruitment process in the Peritoneal VAC trial, in which out of 63 potentially eligible patients, 45 (71%) were recruited over 15 months. Reasons for non-recruitment included patients undergoing gynecological procedures and rescue laparotomies outside of a regular operating room. In the Peritoneal VAC trial, 53% of patients were non-traumatic, and thus a similar range of recruitment would be expected for this trial with thus at least 27 patients recruited per year as a conservative estimate. As the COOL study will extend the option of OA with ANPTT to a greater cohort of SIAS more than 27 patients per year may be expected.

Partner Hospitals in the Regional System

The Calgary Zone of the Alberta Health Services is Regionalized, such that many standards, protocols, and staff are shared between freely communicating and co-operating hospitals. The care of SIAS is provided at three other hospitals, the Peter Loughhead, the Rockyview, and the South Health Campus. These three institutions will all be invited to participate in the COOL study.

Partner Hospitals Globally

It is anticipated that members of both the Abdominal Compartment Society (www.wsacs.org) and the World Society of Emergency Surgery (https://www.wses.org.uk/) will engage their own hospitals as study sites. Although all such sites will be encouraged to participate in COOL-MAX, they may elect to participate in COOL-LITE, in regards to recruiting for the primary mortality outcome.

Learning from the Peritoneal VAC Trial

The investigators and the scientific community have extensively reviewed and critiqued the results of the preceding Peritoneal VAC trial(122). Methodologic concerns with the Peritoneal VAC trial were that it enrolled quite heterogeneous patients with a wide range of ages and included traumatized patients with an exactly known time of injury and severe IAS patients in whom the timing of onset of severe disease was inexactly known. Thus, the COOL-MAX/LITE trial will focus on a more heterogeneous group of patients with intra-operatively confirmed SIAS in order to increase the signal to noise ratio. IL-6 continues to be considered a critical mediator if systemic inflammation and was an appropriate primary endpoint for a trial not expected to show a mortality difference. However, IL-6 levels are rapidly dynamic and important changes (in IL-6 and other important Biomediators) may have occurred that were not captured by a 24 hour early sampling window and thus more samples will be determined earlier in the study.

Randomization and Data Collection

Randomization shall be through a treatment allocation generator hosted on the research page of a dedicated research website replicating the previously successful methodology from the Peritoneal VAC trial. This site is freely open to the public. The ability to enroll a patient however, can only be accessed with a Password by any 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 website will be accessed, simple identifiers of the patient will be entered, and treatment allocation (CLOSED with fascial closure or OPEN with AbTHera placement) 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.

At the lead site (FMC) 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 Nurses of the Department of Critical Care Medicine may assist in this task while patients are being cared for in the ICU, but the Research Manager of Regional Trauma Services will be responsible for overseeing the complete data collection from all patients at FMC from admission to discharge/death.

The collection and completion of data forms at all other contributing sites will be an Institutional requirement with local solutions required. All completed case report forms will be uploaded to a central Database administered by the Research Manager of RTS in Calgary. All contributing sites will be required to collect all appropriate blood samples if participating in COOL-MAX. All such samples will be sent to the Snyder Laboratory/Research Centre in Calgary for central processing.

Clinical Management Protocols

After enrolment and allocation of abdominal compartment management in the operating theatre, all care will be at the complete discretion of the clinical teams.   If the treating physicians decide that a CLOSED abdomen requires re-opening, participation in the study will not influence this decision in any way. However, this will be an outcome and the case will still be analyzed as CLOSED in the primary intention to treat analysis. The timing of re-operation for an OPEN abdomen will at the discretion of the treating physicians and not dictated by this trial although the planned secondary determinations of Biomediator profiles will be analyzed on a per-protocol basis only for patients that had at least 24 hours of continuous OPEN or CLOSED management as allocated.

Proposed Study Sites

1) University of Calgary, Calgary, Canada
2) Helsinki University, Helsinki, Finland
3) University of Newcastle, Newcastle, Australia
4) Unicamp Campinas, Campinas, Brazil
5) Rambam Health Care Campus, Haifa, Israel
6) Niguarda Hospital, Milan, Italy
7) Westchester Medical Centre, Westchester, Massachuscets, USA
8) Letterkenney Hospital, Donegal, Ireland
9) Sherbrooke University, Sherbrooke, Quebec, Canada
10) Maggiore Hospital, Italy
11) IRCCS Policlinico San Donato, Italy
12) Nanjing University, Nanjing, China
13) Papa Giovanni XXIII, Bergamo, Italy
14) St Michaels Hospital, Toronto, Canada
15) R Adams Cowley Shock Trauma Centre, Baltimore, Maryland, USA
16) Scripps Memorial Hospital, San Diego, California, USA
17) University of Auckland, Auckland, New Zealand
18) University of Ottawa, Ottawa, Ontario, Canada

Appendices

Appendix A The Research Team and Prior Relevant Research

Appendix B

Appendix A

The Research Team and Prior Relevant Research

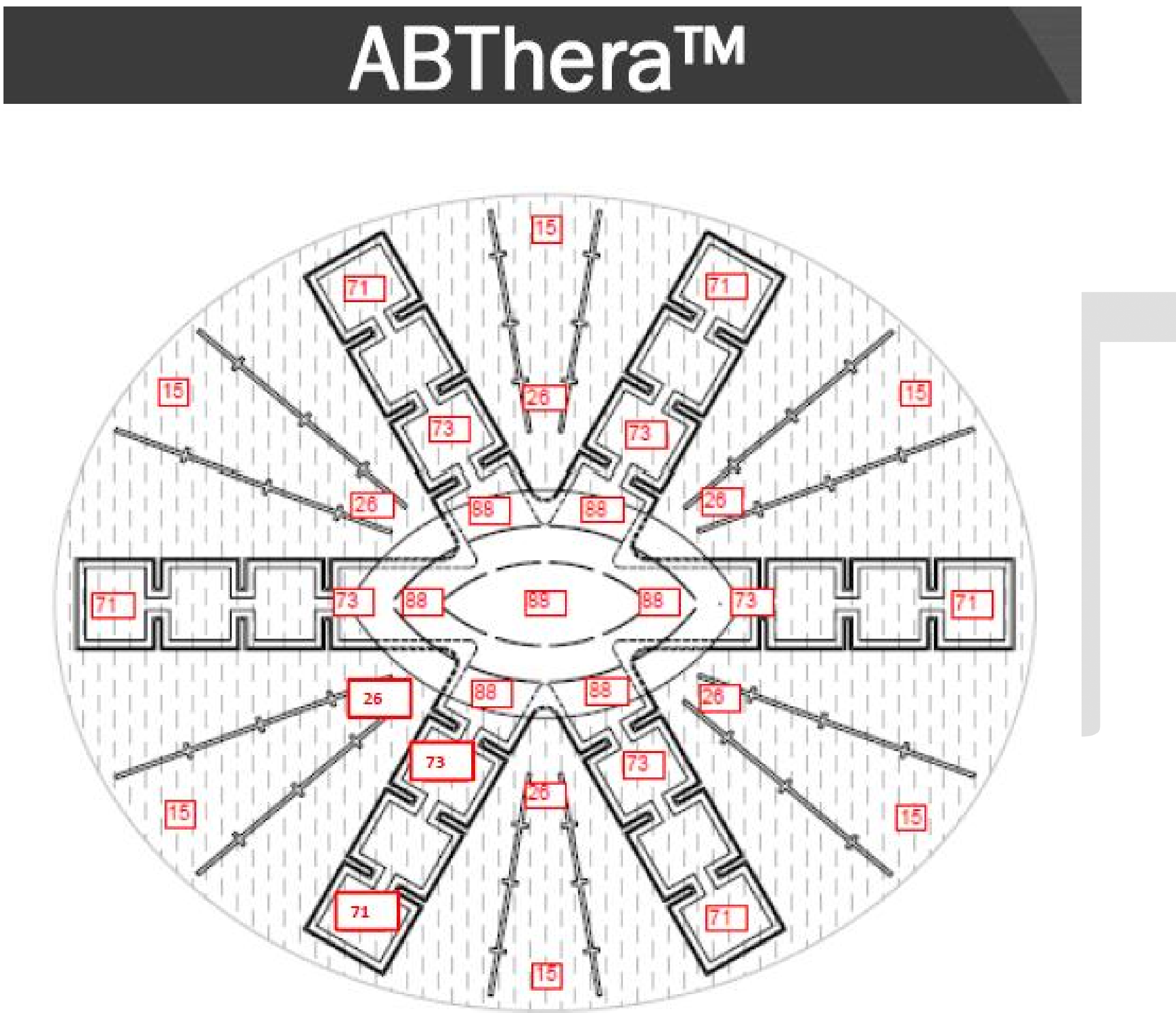
This research study project aims to take leverage the collective inputs of clinicians, scientists, and scholars worldwide to answer a difficult but fundamentally important question concerning severe intra-abdominal infection. The results are expected to have both great clinical as well as basic science importance. The two sponsoring Societies are the Abdominal Compartment Society (http://www.wsacs.org/) and the World Society of Emergency Surgery (https://www.wses.org.uk/). These are global medical societies interested in severe intra-abdominal infection and the pathophysiology and treatment of such within the abdominal compartment. Both societies and their memberships have authored numerous original scientific studies and consensus management guidelines on this topic(13, 15-17, 118, 123, 124), and both have identified this question as crucial to advancing care.

Locally, the lead hospital is ideally suited to leverage our previous work and to continue the tremendous cooperative relationship between clinical care and basic science. The basic science team of Dr. Paul Kubes, director of the Calvin, Phoebe and Joan Snyder Institute of Infection, Immunity and Inflammation (http://www.snyder.ucalgary.ca/) 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 15 years, and hopes to continue to leverage the elegant basic science of Dr Kubes team to assist with their practical surgical knowledge as was done with the Peritoneal VAC study(48, 80, 122). This surgical critical care group has previously studied/described methods of diagnosis and measurement of IAP(115-117, 125-131), studied it's bedside interpretation(132-135), as well as extensively reviewed the literature(43, 128, 136-152). Further, members of our research group sit on the Executive, including the position of the President of Abdominal Compartment Society and have co-authored Society-based consensus documents and statements(27, 40, 153-156).

Appendices and Figures

Appendix A **Physical characteristics of Model TAC dressings**



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

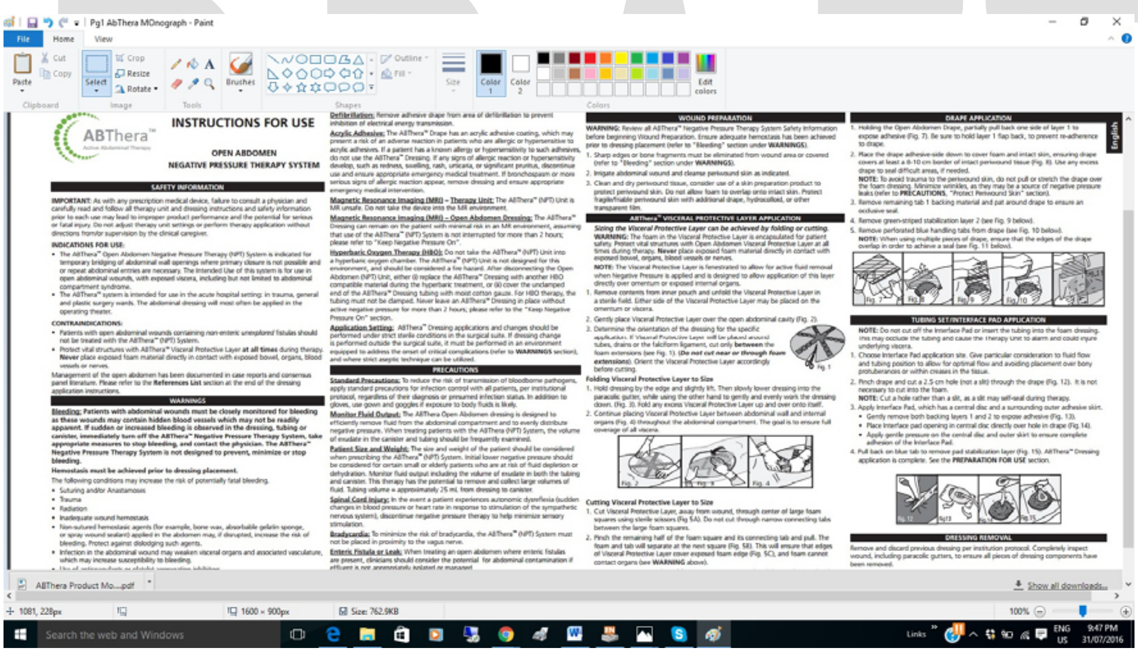
Appendix B

OPEN Closure

Definition and Protocol for use Active-Negative Pressure Peritoneal Therapy

Supplies Required

The ANPPT dressing will be applied intra-operatively according to the manufacturers recommendations for use



(http://www.kci-medical.com/cs/BlobServer?blobheadername3=MDT-Type&blobcol=urldata&blobtable=MungoBlobs&blobheadervalue2=inline%3B+filename%3D145%252F245%252FABThera%2B%2BInstructions%2Bfor%2BUse%2B%2528IFU%2529.pdf&blobheadername2=Content-disposition&blobheadervalue1=application%2Fpdf&blobkey=id&blobheadername1=Content-type&blobwhere=1226669816406&blobheadervalue3=abinary%3B+charset%3DUTF-8).

In addition to compliance with the Manufacturers Recommendations, the study protocol will emphasize;

- Placement of the AbThera dressing deep within the intra-peritoneal gutters
- Use of the un-cut dressing **OR** cutting the foam pieces well within (at least 1 ½ nodes) within the remaining plastic viscero-protective seal

Appendix C

CLOSED Closure

Definition and Protocol for formal fascial closure use Active-Negative Pressure Peritoneal Therapy

Fascial closure

For those randomized to fascial closure, the attending surgeon may select any suture material desired and may close with any technique desired as long as the fascia is formally closed. Closure or not of the skin will be at the discretion of the attending physician, as will be the use or not of any commercial wound sealing devices.

Appendix D Detailed Definitions of Physiological Outcomes Variables

Systemic inflammatory marker levels (e.g. TNF-α, IL-1β, IL-6, IL-10)	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 nomal level. Reference - (157)
Peritoneal fluid inflammatory marker levels (e.g. TNF-α, IL-1β, IL-6, IL-10)	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 (157)
APACHE II score	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 - (158)
SOFA score	Sepsis related Organ Failure Assessment. Describes organ dysfunction/failure, computed based on respiratory, coagulation, cardiovascular, GCS, liver and renal variables (Table D4). Reference - (159)
FiO2/PaO2 ratio	Index to characterize the acute respiratory distress syndrome
Oxygenation Index	(FiO2 * Mean Airway Pressure) / PaO2
RIFLE score	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 - (160-162)**
IAP	Intra-Abdominal Pressure. Pressure concealed within the abdominal cavity; expressed in mmHg. Normal IAP is ~ 5-7 mmHg in critically ill adults.
IAH	Intra-Abdominal Hypertension. Sustained or repeated pathologic elevation of IAP>=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 - (153)

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
Temperature (Rectal/Core) Oral: add 0.5ºC Axilla: add 1.0 ºC		≥ 41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤ 29.9
Mean Arterial Pressure (mmHg)		≥ 160	130-159	110-129		70-109		50-69		≤ 49
Heart Rate		≥ 180	140-179	110-139		70-109		55-69	40-54	≤ 39
Respiratory Rate Non-ventilated or ventilated		≥ 50	35-49		25-34	12-24	10-11	6-9		≤ 5
Oxygenation a) $FiO_2 \geq .5$, record $AaDO_2$		≥ 500	350-499	200-349		< 200	AaDO2 : $[FiO_2 \times 713]-[PaCO_2 \div 0.8]- PaO_2$			
b) FiO2 < .5, record only PaO_2						> 70	61-70		55-60	< 55
Arterial pH		≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum Sodium (mmol/L)		≥180	160-179	155-159	150-154	130-149		120-129	111-119	<110
Serum Potassium (mmol/L)		≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Serum Creatinine (µmol/L)	*	≥309	177 - 308	132-176		53-131		<53		
		*DOUBLE SCORE FOR ARF								
Hematocrit (%)		≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
WBC		≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
GCS (Score=15 minus actual GCS)		Enter Actual GCS here ________								
***HCO_3** (Venous mMol/L) (*Only if no ABG)		≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15
TOTAL PHYSIOLOGIC SCORE										

Reference - (158, 163)

Table D2

Age Points

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

Table D3

Chronic Health Points

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

SOFA score	**1**	**2**	**3**	**4**
Respiration PaO2/FiO2 mmHg	<400	<300	<200 ---with respiratory support----	<100
Coagulation Platelets X $10^3/mm^3$	<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 (μmol/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 - (159)

Table D5

RIFLE Category	Glomerular Filtration Rate	Urine Output Criteria
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 >=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 - (160-162)

Appendix E Detailed Definitions of other baseline and follow-up data

Demographic data	
Sabadell modification of the McCabe score	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)
Admission injury severity data	
AIS	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 - (164, 165)
ISS	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 (166)
RTS	Revised Trauma Score. Physiological index of injury severity, calculated from GCS, systolic blood pressure (SBP) and respiratory rate (RR). These values are multiplies 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 - (167, 168)
GCS	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 - (169-171)
Physiologic and laboratory data	
FiO2/PaO2 ratio	Index to characterize the acute respiratory distress syndrome.
IAP	Intra-Abdominal Pressure. Pressure concealed within the abdominal cavity; expressed in mmHg. Normal IAP is ~ 5-7 mmHg in critically ill adults.
IAH	Intra-Abdominal Hypertension. Sustained or repeated pathologic elevation of IAP>=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 - (153)

Table E1

Sabadell score	Prognosis	ICU readmission
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

AIS Code	Description
1	Minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Maximum

Table E4

Total score of the GCS

Eye Opening Response	Motor Response	Verbal Response
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

Participating Centres

- University of Calgary, Calgary, Canada
- Helsinki University, Helsinki, Finland
- University of Newcastle, Newcastle, Australia
- Unicamp Campinas, Campinas, Brazil
- Rambam Health Care Campus, Haifa, Israel
- Niguarda Hospital, Milan, Italy
- Westchester Medical Centre, Massachusetts, USA
- Letterkenney Hospital, Donegal, Ireland
- Sherbrooke University, Sherbrooke, Quebec, Canada
- Maggiore Hospital, Italy
- IRCCS Policlinico San Donato, Italy
- Nanjing University, China
- Papa Giovanni XXIII, Italy
- St Michaels Hospital, Toronto, Canada
- R Adams Cowley Shock Trauma Centre, Baltimore, Maryland, USA
- Scripps Memorial Hospital, San Diego, California, USA
- University of Auckland, Auckland, New Zealand
- University of Ottawa, Ottawa, Canada

Appendix F **World Society of Emergency Surgery Sepsis Severity Score for patients with complicated intra-abdominal sepsis**

Table 5 WSES sepsis severity score for patients with complicated Intra-abdominal infections (Range: 0–18)

Clinical condition at the admission	
• Severe sepsis (acute organ dysfunction) at the admission	3 score
• Septic shock (acute circulatory failure characterized by persistent arterial hypotension. It always requires vasopressor agents) at the admission	5 score
Setting of acquisition	
• Healthcare associated infection	2 score
Origin of the IAIs	
• Colonic non-diverticular perforation peritonitis	2 score
• Small bowel perforation peritonitis	3 score
• Diverticular diffuse peritonitis	2 score
• Post-operative diffuse peritonitis	2 score
Delay in source control	
• Delayed initial intervention [Preoperative duration of peritonitis (localized or diffuse) > 24 h)]	3 score
Risk factors	
• Age>70	2 score
• Immunosuppression (chronic glucocorticoids, immunosuppresant agents, chemotherapy, lymphatic diseases, virus)	3 score

From Sartelli; World J Emerg Surg 2015(14)

Appendix ZZZ **Calgary PIRO Score for predicting mortality of intra-abdominal sepsis**

Table 4. PIRO Score.

Score	Variable	Point
Predisposition	Age > 65 years	1
	Comorbidities	1
Response	Leukopenia	1
	Hypothermia	1
Organ Dysfunction	Cardiovascular dysfunction	1
	Respiratory dysfunction	1
	Renal dysfunction	1
	CNS dysfunction	1
Total		8

Comorbidities are score as Yes or No based on these Chronic Health Problems:

1) Cirrhosis of the liver confirmed by biopsy

2) New York Heart Association Class IV

3) Severe COPD -- Hypercapnia, home O2 use, or pulmonary hypertension

4) On regular dialysis or

5) Immunocompromised

Organ Dysfunction is Based on the SOFA score values with ≥ 2 as scored using the standard SOFA criteria for cardiovascular, respiratory, renal, and central nervous system function.

Cardiovascular SOFA scoring

Cardiovascular system [edit]

Mean arterial pressure OR administration of vasopressors required	SOFA score
MAP ≥ 70 mm/Hg	0
MAP < 70 mm/Hg	1
dopamine ≤ 5 μg/kg/min or dobutamine (any dose)	2
dopamine > 5 μg/kg/min OR epinephrine ≤ 0.1 μg/kg/min OR norepinephrine ≤ 0.1 μg/kg/min	3
dopamine > 15 μg/kg/min OR epinephrine > 0.1 μg/kg/min OR norepinephrine > 0.1 μg/kg/min	4

Respiratory SOFA Scoring

Respiratory system [edit]

PaO_2/FiO_2 (mmHg)	SOFA score
≥ 400	0
< 400	1
< 300	2
< 200 **and** mechanically ventilated	3
< 100 **and** mechanically ventilated	4

Renal SOFA Scoring

Kidneys [edit]

Creatinine (mg/dl) [µmol/L] (or urine output)	SOFA score
< 1.2 [< 110]	0
1.2–1.9 [110-170]	1
2.0–3.4 [171-299]	2
3.5–4.9 [300-440] (or < 500 ml/d)	3
> 5.0 [> 440] (or < 200 ml/d)	4

Neurological SOFA Scoring

Nervous system [edit]

Glasgow coma scale	SOFA score
15	0
13–14	1
10–12	2
6–9	3
< 6	4

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Appendix 1

Sample size for comparing Event Rates between two Independent Cohorts

How: Place the 2 anticipated proportions/event rates in the appropriate text boxes, and click the Calculate button. The results will show. Note that proportions are entered as a number between 0 and 1, so that 25% is entered as 0.25.

0.42 Estimated proportion in Group 1 (Controls)

0.25 Estimated proportion in Group 2 (Study)

1 Ratio Controls to Experiment Subjects

Calculate

Sample size Estimates per Group for 2 Sided Test assuming two groups are independent

Assuming outcome data will be analysed Prospectively by Uncorrected Chi-square test

	Type I error=0.05	Type I error=0.01	Type I error=0.001
Power=80%	120	179	262
Power=90%	160	227	320
Power=99%	279	365	480

Fishers Exact Sample size estimates per Group for 2 Sided Test assuming two groups are independent

Assuming outcome data will be analysed Prospectively by Fisher's exact-test or with a continuity corrected chi-squared test

	Type I error=0.05	Type I error=0.01	Type I error=0.001
Power=80%	132	191	274
Power=90%	172	239	331
Power=99%	290	377	492

Reference: Casagrande JT, Pike MC, Smith PG. An improved approximate formula for calculating sample sizes for comparing two binomial distributions. Biometrics 1978;34:483-486.
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Formulae on which the estimated sample size is calculated

$$n = \frac{\left[Z_{\alpha}\sqrt{(1+1/m)\,\overline{p}(1-\overline{p})} + Z_{\beta}\sqrt{p_0(1-p_0)/m + p_1(1-p_1)}\right]^2}{(p_0 - p_1)^2}$$

$$\overline{p} = \frac{p_1 + m\,p_0}{m+1} \qquad n_c = \frac{n}{4}\left(1 + \sqrt{1\frac{2(m+1)}{n\,m\left|p_0 - p_1\right|}}\right)^2$$

p0 = Probability of event in Control Group
p1 = Probability of event in Experimental Group
m = Ratio of controls to experiment subjects
nc = Continuity correction factor