# A Novel Wound Retractor Combining Continuous Irrigation and Barrier Protection Reduces Incisional Contamination and Surgical Site Infection in Colorectal Surgery

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**Principal Investigator:** Scott Steele, M.D.
Digestive Disease and Surgery Institute
9500 Euclid Avenue A30
Cleveland, Ohio 44195
Tel: 216 444-4715
Email: steeles3@ccf.org

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## 1. BACKGROUND

Surgical site infection (SSI) remains a persistent and morbid problem in colorectal surgery with published rates ranging from 7 to 25% [1-6]. The negative outcomes of SSI are well reported and include a significant increase in morbidity, length of hospital stay, readmissions and healthcare-associated cost[7, 8]. Therefore, strategies to reduce the incidence of SSI following colorectal surgery are important to improve overall patient outcomes, reduce healthcare-associated costs and provide value-based healthcare to surgical patients.

Since 2005, our institution has been an active participant of the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP), and our SSI rates have been compared with other NSQIP centers; in 2006, we were found to be a high-outlier institution for SSI [9]. The ACS-NSQIP greatly facilitated our understanding of the reasons behind our high SSI rates, the patient profiles that are associated with SSIs, and how we can make improvements. This previously published work helped us to develop a Surgical Site Infection Prevention Bundle to reduce SSI rates after colorectal surgical procedures performed at the Cleveland Clinic. This bundle was introduced in February 2014. Between 2013 and 2015, 2250 abdominal colorectal surgical procedures were performed, including 986 (43.8%) during the prebundle period and 1264 (56.2%) after the bundle project. Patient characteristics and comorbidities were similar in both periods. The overall surgical site infection rate decreased from 11.8% prebundle to 6.6% at the bundle period ($P < 0.001$). Although a decrease for all types of surgical site infections was observed after the implementation, a significant reduction was achieved in the organ-space subgroup (5.5%–1.7%; $P < 0.001$). Since then, the elements of this bundle became the standard of care in all elective colorectal surgeries done at the Cleveland Clinic. The most important elements of the bundle include mechanical bowel preparation, antimicrobial antiseptic skin cleanser, prophylactic antibiotic (ceftriaxone + Flagyl) 1 hour prior to incision, wound irrigation with normal saline, and the usage of wound protector. The outcomes of this SSI prevention bundle was recently published[10]. Although this study was not designed to pinpoint the relative weight of each of these elements in reducing SSIs, participating colorectal surgeons at our institute accredit a big role for wound protectors and irrigation along with prophylactic antibiotics.

Key to the pathogenesis of SSI is the degree of intraoperative bacterial contamination of the surgical wound. Preventing contamination of the wound or reducing the bacterial load through the use of barrier wound protectors or intraoperative wound irrigation has shown significant promise individually and is an ongoing strategic focus to reduce wound infections after surgery [11-13]. A similar role can be attributed to prophylactic antibiotics administered within one hour prior fist incision.

The importance of wound protectors and intraoperative wound irrigation can be elucidated by examining published meta-analyses. The first represented 6 randomized clinical trials (RCTs) and 1008 patients evaluated for the effect of wound protectors in reducing the risk of surgical site infection (SSI) after gastrointestinal surgery. A significant decrease in SSI rates (RR = 0.55, 95% confidence Interval (CI) 0.31-0.98, $P = 0.04$) was noted[13]. A more recent meta-analysis included eighteen randomized controlled trials with 3808 patients. The use of wound protectors was associated with the reduced incidence of overall SSI (OR 0.59; 95% CI 0.43-0.81; $z = 3.30$;

$p < 0.001$) and superficial SSI (OR 0.42; 95% CI 0.18-0.95; $z = 2.09$; $p < 0.04$). In addition, wound protectors successfully reduced the risk of SSI in clean-contaminated wounds (OR 0.67; 95% CI 0.46-0.98; $z = 2.06$; $p < 0.04$) as well as in contaminated wounds (OR 0.24; 95% CI 0.12-0.49; $z = 3.96$; $p < 0.0001$)[11]. Based on that, the WHO global guidelines for the prevention of surgical site infection recommends the usage of wound protector devices in clean-contaminated, contaminated and dirty abdominal surgical procedures for the purpose of reducing the rate of SSI[14].

The usage of intraoperative wound irrigation has also been shown to significantly reduce the risk of SSI via multiple RTC. A significant reduction in SSI rates after intraoperative wound irrigation with any solution was noted compared to no irrigation (OR = 0.54, 95 % CI 0.42; 0.69, $p < 0.0001$) [13].

A surgical device that combines continuous wound irrigation and barrier protection will have an important SSI prevention advantage. CleanCision is a recently developed apparatus that serves this dual purpose and was found to reduce bacterial wound contamination in preclinical and clinical trials. A prospective multicenter pilot study was conducted by colorectal surgeons at 7 large tertiary-care referral centers in the USA[15]. The study was designed to evaluate the bacteriology of the wound incision edge when an investigational device (CleanCision wound protector) that combines continuous wound irrigation and barrier protection was used during colorectal surgery. A total of 97 patients (11 roll-in and 86 treatments) were enrolled in the study. All patients completed the 30-day follow-up. The 86 treatment patients were used for the primary analysis. Use of the study device was associated with a 71% reduction in enteric bacterial contamination (9.5% vs 33.3%, $P < 0.001$), and 66% reduction in overall bacterial contamination (11.9 vs. 34.5%, $P < 0.001$) at the protected incision edge versus the exposed incision edge. In addition, analysis of the skin organisms on the incision edge prior to device placement compared to the protected incision edge at the time of device removal demonstrated an 86% reduction after use of the study device (16.7 vs. 2.4%, $P < 0.001$). There were no deaths and no device-related adverse events reported in the study. There were 4 wound-related adverse events, other than SSI, reported: 1 skin necrosis, 1 non-infections erythema, 1 hematoma and 1 wound opening up postoperatively. All 4 events were not device related as determined by the site investigator. Although SSI was not the endpoint that this study was designed to examine, the observed overall SSI rate was 1.2%, such rate is lower than reported at our institute for colorectal surgery (6.6%)[15].

As part of our continuous effort to reduce SSI, additional measures such as CleanCision wound protector could bring our SSI rates even further. This will translate in better patient care and reduced health care cost.

Supported by the previously published multicenter clinical trial [11, 13, 15], this study aims to investigate the effect of using CleanCision wound protector on the rates of postoperative Surgical Site Infections in comparison to the current wound protector (Alexis O) being used at our institute.

## 2. STUDY OBJECTIVE

To evaluate the 30 day post-operative SSI rate in patients undergoing elective colorectal surgical procedures after intraoperative usage of Alexis O wound protector vs. CleanCision continuous irrigation wound protector.

## 3. SELECTION OF PATIENTS

### 3.1 Inclusion Criteria

- Patients 18 years old and above.
- Elective colorectal surgery with a planned resection including open or laparoscopic surgeries.
- Patients with a clean –contaminated, contaminated, or dirty wound classification
- Patients undergoing Standard of care SSI reduction bundle including Prophylactic AB and mechanical bowel preparation.
- Anticipated incision length of 3-17 cm

### 3.2 Exclusion Criteria

- Patients with a preexisting stoma.
- Patients with prior laparotomy within 15 days.
- Patients with an active infection or systemic antibiotic therapy within 1 week prior to surgery with the exception of preoperative antimicrobial prophylaxis.
- Emergent/ urgent surgery.

### 3.3 Statistical Considerations

Planned Data Analysis

Descriptive statistics will be computed for all variables including mean ± standard deviation or median [25th, 75th percentiles] for continuous factors and frequency (percent) for categorical variables. Univariate analyses will be conducted to compare the distribution of pre-op characteristics across study groups using ANOVA for continuous variables and Chi-square or Fisher's exact test for categorical variables.

For purposes of statistical analysis, a subset analysis may be done based on laparoscopic vs. open procedures, patients with high risk for SSI, type of surgery, or other clinically significant co-factors. All data will be analyzed with the use of SAS (version 9.4, The SAS Institute, Cary, NC), SPSS statistical software (SPSS Inc., Chicago, IL), or R version 3.1.2 (www.R-project.org). A p-value $<0.05$ will considered statistically significant.

Sample Size Calculations

The sample size calculation using estimates of SSIs from the Papaconstantinou et al. Multicenter trial. This study showed an incisional SSI rate of 1.2% in those that completed the protocol. In comparison, the incisional SSI rate using the current standard of care

practice at our institute is 4.8 %. On the other hand, the overall SSI rates in Papaconstantinou et al. multicenter trial is 3.7% and in the current standard of practice at the Cleveland Clinic, the overall SSI rate is 6.6%. We used these two estimates of SSI rates to calculate the sample size. Using the incisional SSI, we assumed a 3.6% drop rate if the study hypothesis is true. We are assuming equal-sized treatment groups and alpha = 0.05. Based on this assumption, a total of 277 subjects in each study group will be needed to achieve 70% power, 351 subjects in each study group will be needed to achieve 80% power, and 470 subjects will be needed to achieve 90% power. On the other hand, using the overall SSI rates and assuming a drop of 2.9% , a total of 716 subjects in each study group will be needed to achieve 70% power, 805 subjects in each study group will be needed to achieve 80% power, and 1219 subjects will be needed to achieve 90% power.

Based on the above, 351 patients will be enrolled in the study in each arm with a total of 702 patients.

Reporting of Results
Aggregate and anonymous, in text and table format, for publication in a medical journal.

## 4. STUDY DESIGN

This industry-initiated trial will be a prospective randomized controlled trial. The study will include patients undergoing elective colorectal surgical procedures. All patients will receive the standard of care SSI prevention bundle. Part of this bundle is the utilization of wound protectors. The current system used at Cleveland Clinic is Alexis wound protectors/retractors (Applied Medical, Avenida Empresa Rancho Santa Margarita, CA). It provides 360° of circumferential, atraumatic dry retraction. Independent wound irrigation is also utilized. CleanCision is a novel FDA approved irrigating wound protector/ retractor that combines mechanical wound protection with an active continuous irrigation via microfluidic system that circulates the irrigation throughout the whole thickness of the protecting membrane. The safety and possible advantage of this new system has been shown through preclinical and clinical studies. Prescient Surgical, based in San Carlos, California, has an FDA marketing clearance for its CleanCision Wound Retraction and Protection System.

### 4.1 Consent

Patients will be identified prospectively by the treating surgeon according to the inclusion / exclusion criteria. Patients will be offered to participate in the study in the preoperative setting. The patient eligibility to participate in the study will be verified by the study team. The study details will be explained to the patient by a member of the study team. The consent conversation will take place in a private room and a sufficient time interval will be offered to allow the patient to comprehend the study details. Enrolled patients will be randomly assigned via REDCap in a 1:1 ratio to either the control arm (Alexis wound protector) or the intervention arm (CleanCision Wound retractor system). The randomization will be done by a delegated member of the study team. Consent will be documented in the medical record.

4.2 Study Process

Utilization of CleanCision wound protector/ Irrigation system is free of charge without extra financial charges to the enrolled patients.

The study team will confirm that patients are adhering to pre- intra- and post-operative standard of care SSI prevention bundle. The Bundle main elements are:

- Patient bathing with Hibiclens preoperatively.
- The patient use CHG (SAGE) wipes.
- Mechanical bowel preparation.
- Antibiotics Prophylaxis (ceftriaxone + Flagyl) given approximately 1 hour prior to incision. If the patient is allergic to above antibiotics, aztreonam or imipenem are used as prophylactic antibiotics.
- The usage of wound protector and the placement and removal of blue towels under the Alexis wound protectors for control cases.
- Use chlorhexidine gluconate and isopropyl alcohol for preoperative skin preparation
- Wound irrigated with 100cc of fresh saline.
- Separate instrument tray used for closing the incision.
- Gloves changed before closing the incision.
- Suction tip changed before closing the incision.
- Dressing left intact for 48 hours postop.

The usage of a wound protector along with wound irrigation intra-operatively is considered standard of care. This study entails utilizing two type of wound protectors, both are considered standard of care in terms of providing the baseline needed protection. Intra-operatively, either CleanCision Wound protector/ irrigation system or Alexis O wound protector will be chosen. Additional wound irrigation and washing with Normal Saline will be performed before skin closure as part of the standard of care. This will include both study groups (patients with Alexis O wound protectors and CleanCision wound protectors). In the CleanCision group, a broad spectrum antibiotic may be added to the irrigation fluid. Post-operatively, patients will be followed for wound infections according to the standard of care in the department of colorectal surgery. For patients undergoing colorectal procedures at the department of colorectal surgery, the timing of outpatient post-operative follow-up can be variable depending on the type of procedure performed, the treating surgeon, the patient place of residence, and the patient general medical condition. To avoid variability, patients will be asked to send a photographic documentation of the wound at day 7 ± 7 days and day 30 ± 7 days postoperatively to the study team. The photographs will be stored in the secure REDCap database. If a patient presents for follow-up at the outpatient clinic at the above time points and as part of standard of care, a photograph of the wound can be obtained during the outpatient visit by the study team member. The purpose of these photographs as well as the time points will be explained to the patient at the time study enrollment. Patients refusing or incapable of sending the photographs will not be enrolled in the study. For study enrolled patients' a reminder will be added to the hospital discharge note asking the patient to send the photographs to the above email address at the corresponding time points.

### 4.3 Blinded Assessment

The study team member will evaluate the images for signs of surgical site infection and will be blinded to the type of wound protector used intraoperatively. This will be done at regular intervals and in aggregate.

### 4.4 Data Recording

Data will be collected from EPIC by the study team. A secure REDCap database will be utilized to store the data. The following variables will be recorded:

A) Preoperative variables:

- Patient Demographics:
  - DOB, age at the time of surgery, gender, race, Height, weight and body mass index (BMI) at the time of surgery.
- American Society of Anesthesiologists physical status classification (ASA score).
- Preoperative diagnosis and patient's History of present illness.
- Adherence to SSI prevention bundle (elements defined above).
- Risk factors for SSI including nutritional status (represented by patient current weight) and immune status including WBC and differentials, history of smoking, and any other risk factors for SSI.

B) Intraoperative variables:

- Operating surgeon.
- Length of incision/wound.
- Surgical approach (open vs. laparoscopic vs transanal).
- Device deficiencies including (leaking of fluid, breakage of plastic sheath, ring malfunction in CleanCision wound protector).

C) Postoperative variables:

- In-patient Progress notes.
- The development of SSI per the criteria defined above along with any related investigation / clinical encounter needed for such diagnosis. The timing of SSI development.

### 4.5 Definitions

The World Health Organization (WHO) definitions of wound classifications and SSIs were adopted in this study. The WHO definitions are based on the Center for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN). NHSN is the nation's most widely used healthcare-associated infection tracking system [14].

*Surgical wound classification*

1. Clean: An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tracts are not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage.

2. Clean-contaminated: Operative wounds in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.

3. Contaminated: Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (for example, open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, non-purulent inflammation is encountered including necrotic tissue without evidence of purulent drainage (for example, dry gangrene) are included in this category.

4. Dirty or infected: Includes old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing post-operative infection were present in the operative field before the operation.

*Surgical Site Infections (SSI)*

*Superficial SSI*
A) An infection occurring within 30 days of the operative procedure (where day 1 = the procedure date).

B) AND involves only skin and subcutaneous tissue of the incision.

C) AND patient has at least one of the following:

- Purulent drainage from the superficial incision.
- Organisms identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment.
- Superficial incision that is deliberately opened by a surgeon or other designee and culture or non-culture based testing is not performed AND patient has at least one of the following signs or symptoms: pain or tenderness; localized swelling; erythema; or heat.
- Diagnosis of a superficial incisional SSI by the surgeon or other designee.

The following do not qualify as superficial SSI:

- Diagnosis/treatment of cellulitis (redness/warmth/swelling), by itself, does not meet criterion “d” for superficial incisional SSI. Conversely, an incision that is draining or that has organisms identified by culture or non-culture based testing is not considered a cellulitis.
- A stitch abscess alone (minimal inflammation and discharge confined to the points of suture penetration).

- A localized stab wound or pin site infection- Such an infection might be considered either a skin or soft tissue infection, depending on its depth, but not an SSI.

*Deep SSI*
A) An infection occurring within 30 days of the operative procedure (where day 1 = the procedure date).

B) AND involves deep soft tissues of the incision (for example, fascia and muscle layers)

C) AND patient has at least one of the following:
- Purulent drainage from the deep incision.
- Deep incision that spontaneously dehisces, or is deliberately opened or aspirated by a surgeon or other designee AND organism is identified by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment or culture or non-culture based microbiologic testing method is not performed AND patient has at least one of the following signs or symptoms: fever (>38°C); localized pain or tenderness. A culture or non-culture based test that has a negative finding does not meet this criterion.
- An abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test.

*Organ/Space SSI*
A) An infection occurring within 30 days of the operative procedure (where day 1 = the procedure date).

B) AND infection involves any part of the body deeper than the fascia/muscle layers that is opened or manipulated during the operative procedure.

C) AND patient has at least one of the following:
- Purulent drainage from a drain that is placed into the organ/space (for example, closed suction drainage system, open drain, T-tube drain, CT guided drainage)
- Organisms are identified from fluid or tissue in the organ/space by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing (ASC/AST).
- An abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test evidence suggestive of infection.

D) AND at least one criterion for a specific organ/space infection site listed below
-Gastrointestinal tract infections, excluding, gastroenteritis and appendicitis, must meet at least one of the following criteria:
1. Patient has one of the following:
    a. An abscess or other evidence of gastrointestinal tract infection on gross anatomic or histopathologic exam.
    b. An abscess or other evidence of gastrointestinal tract infection on gross

anatomic or histopathologic exam.

AND organism(s) identified from blood by a culture or non-culture based microbiologic testing method, which is performed for purposes of clinical diagnosis or treatment.

*Intraabdominal Infection*

1. Patient has organism(s) identified from an abscess or from purulent material from intraabdominal space by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment.
2. Patient has at least one of the following:
   a. An abscess or other evidence of intraabdominal infection on gross anatomic or histopathologic exam.
   b. An abscess or other evidence of intraabdominal infection on gross anatomic or histopathologic exam.

   AND organism(s) identified from blood by a culture or non-culture based microbiologic testing method, which is performed for purposes of clinical diagnosis or treatment.

3. Patient has at least two of the following: fever (>38.0°C), hypotension, nausea, vomiting, abdominal pain or tenderness.
   And at least one of the following:
   a. organism(s) seen on Gram stain and/or identified from intraabdominal fluid or tissue obtained during invasive procedure or from an aseptically-placed drain in the intraabdominal space (for example, closed suction drainage system, open drain, T-tube drain, CT guided drainage) by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment.
   b. Organism(s) identified from blood by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment.
   c. *AND* imaging test evidence suggestive of infection (for example, ultrasound, CT scan, MRI, ERCP, radiolabel scans [gallium, technetium, etc.] or on abdominal x-ray), which if equivocal is supported by clinical correlation, specifically, physician documentation of antimicrobial treatment for intraabdominal infection.

## 5. ADVERSE EVENTS

### 5.1 Definition

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

### 5.2 Reporting Adverse Events

Although we do not anticipate any serious adverse events, all reportable serious adverse events will adhere to the policy guidelines of the IRB and the sponsor, if applicable. All other adverse events associated with surgery in the 30 day post-operative setting will be recorded on an adverse event log and submitted to the Cleveland Clinic IRB on an annual basis.

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