**Direct Peritoneal Resuscitation in Emergency General Surgery: An EAST Multicenter Trial**

This study aims to assess the outcomes of direct peritoneal resuscitation (DPR) for patients undergoing non-traumatic emergency laparotomy, focusing on both the efficacy and safety of this intervention compared to conventional resuscitation (CR). We hypothesize the use of DPR in emergency general surgery for intra-abdominal pathology requiring damage control laparotomy will reduce time to closure and improve primary closure rates, reduce intra-abdominal complications and improve mortality compared to conventional resuscitation strategies. This approach section outlines the aims, hypotheses, inclusion/exclusion criteria, statistical analysis, and how the study will be conducted to evaluate these outcomes.

Aims and Outcomes

*Study Aims:*

1. The primary aim of this study is to evaluate whether DPR can improve primary closure rates compared to conventional resuscitation methods.

2. The secondary aim of this study is to compare DPR versus conventional resuscitation in the following secondary outcomes:
   - Time to closure and number of reoperations.
   - Incidence of intra-abdominal complications.
   - Mortality.

Hypotheses:

We hypothesize that the use of DPR in nontraumatic emergency laparotomy compared to conventional resuscitation will:

- Improve the likelihood of primary closure.
- Decrease time to abdominal closure and reduce the number of subsequent abdominal reoperations.
- Reduce intra-abdominal complications such as infections, abscess formation, or fistulas.
- Result in improved patient survival rates by reducing systemic inflammatory responses and facilitating faster stabilization.

Study Design: Data will be collected from electronic health records.

1. DPR Group: Patients in this group received direct peritoneal resuscitation with or without additional resuscitation measures.
2. Conventional Resuscitation Group: Patients in this group received standard fluid resuscitation methods, which may include intravenous fluids, blood products, and other supportive measures.

*Outcomes:* The study will focus on the following primary, secondary, and tertiary outcomes:

Primary Outcome:

Primary fascial closure: It is hypothesized that DPR will lead to higher rates of primary fascial closure in patients compared to the conventional resuscitation group.

Secondary Outcomes:

1. Time to abdominal closure: The primary hypothesis is that patients undergoing DPR will have significantly shorter time to fascial closure compared to those receiving conventional resuscitation.
2. Number of operations to closure: We hypothesize that patients undergoing DPR will require fewer operations to achieve final abdominal closure compared to those receiving conventional treatment.
3. Intra-abdominal complications: We hypothesize that the DPR group will experience fewer intra-abdominal complications, such as anastomotic leaks, bleeding, abscesses, or enterocutaneous fistula, when compared to the conventional resuscitation cohort.
4. 30-day mortality: We hypothesize there will be lower 30-day mortality in the DPR group.

Tertiary Outcomes:

1. Unplanned reoperation and interventional procedures performed on the abdomen: This will examine if DPR reduces the necessity for additional abdominal interventions.
2. ICU and hospital length of stay (LOS): We hypothesize that the DPR cohort will have reduced ICU and total hospital LOS compared to the conventional resuscitation cohort, potentially reflecting improved outcomes and fewer complications.
3. Resuscitation volume: The total resuscitation required during the initial phase of care and the net volume from index operation to closure will be assessed, with the hypothesis that DPR will require less resuscitation fluid compared to conventional methods.
4. Time on ventilator: We will examine whether DPR patients experience shorter durations on mechanical ventilation compared to those receiving conventional resuscitation.
5. Fascial Dehiscence/Incisional Hernia: We hypothesize lower likelihood of fascial dehiscence and incisional hernia development in the DPR group.

Inclusion Criteria: Patients eligible for inclusion must meet the following criteria:

- Adult patients (≥18 years) undergoing laparotomy for non-traumatic emergency general surgery diagnoses, including intra-abdominal sepsis, bowel perforation, bowel obstruction, pancreatitis, or intra-abdominal hypertension between 01/01/2021 and 12/31/2024
- Patients who require temporary abdominal closure with the need for re-exploration (open abdomen)
- Patients must be managed with either direct peritoneal resuscitation (DPR) or conventional resuscitation during their treatment.

Exclusion Criteria

- Pregnant patients
- Patients under 18 years of age
- Incarcerated individuals at the time of presentation

The study will consist of patients who underwent laparotomy for the above indications with temporary abdominal closure with either peritoneal resuscitation or conventional resuscitation. Patients meeting all the inclusion criteria will be identified from the ICD 10 diagnosis codes and CPT codes within the electronic medical record. The exclusion criteria listed above will be applied, and potential confounding variables will be considered during the statistical analysis.

Variables to be collected: Data will be collected from electronic medical records, focusing on the following key variables (see detailed variables table at end):

- Demographics: Age, gender, race, insurance.
- Clinical Characteristics: Diagnosis at the time of laparotomy, initial presenting condition (e.g., bowel perforation, intra-abdominal sepsis), comorbidities and physiologic data including vitals and labs at both time of index operation and 48 hours.
- Hospital Course and Treatments: Surgical procedures performed, complications during hospitalization, ICU course, length of stay.
- Outcomes of Interest: Data regarding primary fascial closure, time to closure, complications, reoperations, ICU/hospital length of stay, and fluid balance.

Data will be coded and de-identified and kept securely in REDCap. Data will be analyzed, and the results disseminated. Each participating center is responsible for obtaining individual IRB approval to access electronic medical record for each patient who meets the inclusion criteria. Each center will upload de-identified data to a centralized REDCap database supported by Boston University Medical Center. Data use agreements (DUA) will be obtained should a participating institution require a DUA to share de-identified information. Data will then be collated for analysis.

Statistical Analysis Plan

This retrospective cohort study will evaluate the outcomes of DPR versus CR in patients undergoing laparotomy. Continuous variables will be tested for normality using Shapiro-Wilk test and visualized

using histograms. Normally distributed data will be summarized using mean and standardized deviation with non-normal distribution reported using median and interquartile range. Categorical variables will be presented as counts and percentages. Continuous data will be analyzed using T-tests/Mann-Whitney U test, categorical variables will be evaluated using Chi-square test or Fishers exact for n < 5. Chi-square will be used to test the association between a categorical variable with a binary outcome (primary fascial closure, 30-day mortality, complications, interventional procedures, facial dehiscence, hernia: Yes vs No); T-tests/Mann-Whitney U test will be examined to test a continuous variable with a binary outcome; univariate Poisson/univariate negative binomial regression will be tested the association between a covariate and a count outcome (time to abdominal closure (d), number of operations to closure, LOS, ICU-free days, resuscitation volume, time on ventilator). For those covariates with $p<0.05$ from a univariate test will be selected in the final multivariable regression models accordingly. Firth's penalized likelihood option may also be used in a logistic regression if having a rare event.

Sample Size Justification and Power Analysis:

The estimated sample size is 342 patients, with 171 patients per group, based on prior studies. We are planning a study of independent experimental cases and controls. Prior data indicate that the failure rate (no primary fascia closure) among controls (no DPR group) is 0.32 (Barker et al 2007 and Dubose et al 2013). If the true failure rate for experimental subjects is 0.17 (Smith et al, 2017 [83% success primary closure]), we will need to study 171 experimental subjects and 171 control subjects to be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0.9. This sample size provides 90% power to detect a difference in closure rates with a high degree of confidence, while maintaining an acceptable type I error rate (0.05). We will use an uncorrected chi-squared statistic to evaluate this null hypothesis. This is based on the most recent available high-quality data on DPR. We have increased the power to 90% to address concerns about underpowering this study as there is no more current literature and resuscitation techniques have changed.

**The POWER Procedure**
**Pearson Chi-square Test for Proportion Difference**

| Fixed Scenario Elements | |
|---|---|
| **Distribution** | Asymptotic normal |
| **Method** | Normal approximation |
| **Null Proportion Difference** | 0 |
| **Group 1 Proportion** | 0.17 |
| **Group 2 Proportion** | 0.32 |
| **Nominal Power** | 0.9 |
| **Number of Sides** | 2 |
| **Alpha** | 0.05 |

| Computed N per Group | |
|---|---|
| **Actual Power** | **N per Group** |
| 0.901 | 171 |

Handling of Missing Data

Given the retrospective nature of this study, a significant proportion of variables are expected to be missing. Missing data will not be imputed; instead, they will be clearly indicated and accounted for in the analysis.

Confounding and Bias Control

To adjust for potential confounders including, but not limited to age, sex, race, comorbidity index, APACHE II score, Poisson or negative binomial regression, logistic regression will be used when appropriate. Potential confounders with p-values <0.05 from unadjusted analyses will be included in adjusted models.

Propensity Score matching may be utilized to further reduce selection bias. If utilized, the following strategy will be followed: Once the score is estimated based on chosen covariates with modeling probability of having DPR, patients will be matched using one of the following methods: nearest neighbor, caliper, Mahalnobis distance or Inverse probability of treatment weighting. We anticipate using 1:1 nearest neighbor matching with a 0.2 SD of the logit propensity score which will help to minimize bias while maintaining adequate sample size for appropriate power of statistical analyses.

Planned Subgroup Analyses and Sensitivity Analyses

Subgroup analyses will be conducted examining patients presenting with pancreatitis compared to other diagnoses.

If propensity score matching is utilized instead of multivariable regression, we will conduct sensitivity analyses to confirm robustness using alternative caliper widths of 0.1 and 0.3 in addition to comparing the results with the unmatched cohort.

Software:

Statistical analysis will be completed using SAS version 9.4 (SAS Institute Inc.,Cary, NC, USA) or Stata SE version 18 or newer using the packages tefects and psmatch2.

This described approach will allow for evaluation of direct peritoneal resuscitation's impact on primary fascial closure, time to closure, complication rates, mortality and other relevant outcomes in patients undergoing emergency laparotomy. The use of appropriate statistical methods, sample size calculation, and consideration of confounding factors will ensure reliable results.

Enrollment:

We have secured preliminary commitments from the following institutions who regularly perform DPR for EGS and have been doing so consistently.

1. Boston Medical Center – Megan Janeway, MD, Sheina Theodore, MD
2. East Carolina University Health Medical Center - Eric A. Toschlog, MD, Aaron Hudnall, MD, Trisha Aponte (clinical research coordinator)
3. University of Louisville Health – Jason W. Smith, MD
4. The Ohio State University Wexner Medical Center – Carrie Valdez, MD
5. Penn Medicine Lancaster General Health – Amanda Rabideau, MD
6. University of Nebraska Medical Center – Chris Barrett, MD
7. University of Iowa – Samuel Carlson, MD, Dionne Skeete, MD
8. Jackson Health System - Ryder Trauma Center - Nicholas H. Carter, MD

## Specific Aims

Each year, millions of patients worldwide undergo emergency laparotomy for non-traumatic abdominal pathology. In severe intra-abdominal infection, surgical source control is a key component of treatment; however, the mortality rate for these patients remains high, ranging from 23% to 38%. Consequently, any reduction in mortality and morbidity associated with these emergency surgeries has the potential to be impactful.

Prolonged open abdomen following damage control laparotomy is associated with increased risk for complications such as infection, delayed closure, and mortality. Direct peritoneal resuscitation (DPR) has emerged as a promising tool in reducing these risks, with prior studies in trauma populations demonstrating improvements in rates of and time to fascial closure, decreased intra-abdominal abscess formation, lower 30-day mortality, fewer ventilator and fewer ICU days. Despite these findings, the use of DPR in emergency general surgery for patients requiring laparotomy has not been well studied. The best existing evidence on DPR in emergency general surgery is from small trials that have limitations, including; being a single center study; lack of generalizability; and lack of statistical power to examine important secondary outcomes (e.g., 30-day mortality).

An EAST multicenter trial is a unique opportunity to address this gap in knowledge and conduct a larger and more generalizable study of DPR in emergency general surgery. We aim to use the results from this study to contribute to and help inform new clinical guidelines, in alignment with EAST's mission to advance practice and share knowledge. This would represent a critical advancement in standardizing care for resuscitation in patients undergoing laparotomy with potential to improve overall patient outcomes in this high-risk group.

The objective of this study is to assess the efficacy of direct peritoneal resuscitation compared to conventional resuscitation in improving clinical outcomes, including primary fascial closure, time to fascial closure, complications, and mortality, in patients undergoing laparotomy for non-traumatic indications without immediate abdominal closure. We hypothesize that DPR will increase rates of primary fascial closure, improve time to abdominal closure, reduce intra-abdominal complications, and lower 30-day mortality compared to conventional resuscitation strategies. We have the following Specific Aims:

**Aim 1. To compare the efficacy of direct peritoneal resuscitation vs. conventional resuscitation in improving primary fascial closure rates.** We hypothesize DPR will result in a higher likelihood of achieving primary fascial closure compared to conventional resuscitation techniques. We will conduct a retrospective multicenter study utilizing data from electronic medical records to compare outcomes after DPR (vs. conventional resuscitation). We expect that patients in the DPR group will experience higher primary closure rates, contributing to reduced morbidity and improved outcomes. **Aim 2. To examine whether DPR can reduce adverse outcomes and mortality and to identify differences in volume of resuscitation compared to conventional resuscitation that may impact outcomes in patients with open abdomen.** We hypothesize the use of DPR will improve several secondary outcomes, including reducing intra-abdominal complications, mortality, ventilator days, and ICU/hospital length of stay (LOS), compared to conventional resuscitation. We will examine clinical outcomes, physiologic data, and calculate volume of resuscitation derived from the electronic medical record to assess these secondary outcomes. We expect that DPR will be associated with reduced complications and improved recovery metrics (shorter ICU/hospital LOS, fewer ventilator days). **Aim 3. To gather and analyze data that will contribute to evidence-based recommendations for temporary abdominal closure in emergency general surgery and seek funding for a randomized controlled trial (RCT) to validate these findings.** Providing additional and more updated data on strategies for management of the open abdomen in emergency general surgery will help inform management and contribute to current clinical guidelines. This will improve patient care by contributing to standardized resuscitation strategies for laparotomy patients, leading to more consistent and effective management of open abdomen cases. Additionally, this work will pave the way for further studies to validate the use of DPR in EGS in a randomized controlled trial setting.

Conducting an EAST multicenter trial will result in a better understanding of the outcomes of DPR (vs. conventional resuscitation) allowing surgeons to make more informed decisions regarding resuscitation following damage control surgery. This approach will generate new knowledge on best practices and inform individual surgeon approach with the potential for broad applicability in the delivery of care. The study will additionally provide a foundation for future trials studying resuscitation techniques. Lastly, these data will be invaluable for informing clinical guidelines and standardizing care in emergency general surgery with potential to significantly improve patient outcomes.