

**A Randomized Pilot Trial of Dilute Povidone-iodine Irrigation vs No Irrigation for
Children with Acute, Perforated Appendicitis**

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Children with Acute, Perforated Appendicitis**

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STATEMENT OF COMPLIANCE

This study will be conducted according to US and international standards of Good Clinical Practice (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and International Conference on Harmonisation guidelines), applicable government regulations, and institutional research policies and procedures.

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KuoJen Tsao, MD

Principle Investigator

[Redacted Signature]

List of Abbreviations

IAA	Intra-abdominal abscess
CMHH	Children's Memorial Hermann Hospital
PVI	Povidone-iodine (aka. Betadine®)
CT	Computed tomography

Significance

Postoperative intra-abdominal abscesses are common occurrences after perforated appendicitis in pediatric patients despite utilization of evidence-based practices. Povidone-iodine is a commonly used antiseptic in surgical procedures and has been shown to be effective in reducing postoperative abscesses in adults with perforated appendicitis. This trial will be the first to rigorously test the efficacy of povidone-iodine irrigation in children and to verify its safety profile in this patient population.

1.0 Key Roles

KuoJen Tsao, MD: As the Principle Investigator, Dr. Tsao will be responsible for the overall study from the surgical and medication administration perspective, compliance with regulations and ethical standards, patient safety, accuracy of the study results and reporting.

2.0 Background Information and Scientific Rationale

2.1 Background

Acute appendicitis is the most common gastrointestinal-related disease requiring surgery in children. Nearly 25% of all children with perforated appendicitis develop postoperative surgical site infections, specifically intra-abdominal abscesses (IAA), which is likely due to the intra-abdominal sepsis that occurs with the perforated viscus [1,2]. These IAA lead to increased patient discomfort, extended hospital stays, and increased emergency room visits and readmissions [3]. In line with other children's hospitals in the country, Children's Memorial Hermann Hospital (CMHH) has implemented evidence-based practices such as early and culture-directed antibiotic coverage, early operation, and protocol-driven postoperative care [1,2]. Specifically for patients with perforated appendicitis, over the course of four years, our dedicated team of pediatric surgeons has reviewed patient outcomes on an iterative basis, leading to targeted intraoperative and postoperative interventions such as transperitoneal drain placement and customized home antibiotic regimens in an attempt to decrease postoperative IAA. Despite all these efforts, the IAA rate has remained unchanged.

In a 2004 survey of North American pediatric surgeons, over 90% responded that they use intra-abdominal irrigation for patients with advanced appendicitis [4]. However, although its use is widespread, intraoperative irrigation has not been widely studied. There is strong evidence of no difference in IAA rate when no irrigation is compared to normal saline irrigation for children with perforated appendicitis [5], and there is even some evidence that suggests that NS irrigation may actually increase the rate of postoperative IAA [6]. Another irrigation solution that is widely available and commonly used in the operating room is povidone-iodine (PVI). PVI is an antiseptic solution consisting of polyvinylpyrrolidone with water, iodide, and 1% available iodine. It has bactericidal ability against a large array of pathogens, including those pathogens which commonly cause postoperative IAA in children with perforated appendicitis [7,8]. Just a few examples of how PVI is used for surgery include: skin and mucosal preoperative preparation, intestinal intraluminal irrigation prior to division and anastomosis, mediastinal washout following sternal wound infections, and refractory chylothorax in newborns [9–11].

Although PVI is commonly used in pediatric operations, its use as an intra-abdominal irrigant for perforated appendicitis has not been rigorously studied.

A recent meta-analysis demonstrated that intraoperative irrigation with PVI in abdominal, gynecologic, and spinal surgeries significantly decreased postoperative abscesses compared to normal saline irrigation or no irrigation at all (pooled relative risk 0.13, 95%CI 0.05-0.37, $p < 0.001$) [12]. However, of the trials included in this particular analysis, only two of the four focused on treating intra-abdominal sepsis and neither of the studies indicated the number or age of pediatric patients who were enrolled [13,14]. A recent survey of European general adult surgeons found that nearly 40% of them commonly use PVI irrigation for contaminated or dirty abdominal surgeries such as perforated appendicitis [15]. Despite the existing data supporting the efficacy of PVI to reduce IAA and its common use in dirty abdominal surgeries, there have been no recent, high-quality trials demonstrating its effectiveness in reducing IAA after perforated appendicitis in children.

2.2 Scientific Rationale

Hypothesis: Among pediatric patients presenting to CMHH with perforated appendicitis, intra-abdominal irrigation with PVI versus no irrigation will decrease the rate of 30-day postoperative IAA.

Specific Aim 1: To conduct a pilot randomized controlled trial to compare the efficacy of PVI irrigation to no irrigation for decreasing postoperative IAA in children with perforated appendicitis

Specific Aim 2: To verify the safety profile of dilute PVI for intra-abdominal irrigation

Specific Aim 3: To determine the effect of PVI irrigation vs no irrigation on hospital length of stay, readmissions, and cost

2.3 Potential Risks and Benefits

PVI is commonly used in the surgical treatment of adults with dirty abdominal surgeries such as perforated appendicitis [15]. PVI could cause an allergic reaction or iodine toxicity; however, this is exceptionally rare, especially at dilute concentrations [16]. Potential benefits include a reduction in postoperative IAA, decreased length of stay, and fewer readmissions. The

knowledge obtained from this study could help to improve patient outcomes following acute, perforated appendicitis as well as provide preliminary data for a larger, pragmatic trial.

There is a possibility of breach of confidentiality. However, all data collected will be put into a password protected database with will be kept on a password-protected secure server with access limited to study personnel associated with the study.

3.0 Objectives

To determine the effect of PVI irrigation versus no irrigation on the rate of IAA at 30-days post-operative following appendectomy for acute, perforated appendicitis

4.0 Study Design

This will be a single-center, pilot RCT carried out by the Pediatric Surgery Department at UT Houston – CMHH. All UT Houston pediatric surgery attendings will participate. Patients will be randomized to PVI irrigation or no irrigation.

5.0 Study Population

5.1 Selection of the Study Population

A team of five pediatric surgery research coordinators will coordinate the enrollment, consent, and assent processes. The research coordinator team will be available 24/7 to the pediatric surgery service via a dedicated pager. Residents and attendings on the pediatric surgery service will page the research coordinators upon diagnosing a patient with suspected appendicitis. All patients undergoing appendectomy for acute appendicitis will be eligible for the trial. After enrollment, only patients who are diagnosed intraoperatively with perforated appendicitis will be randomized.

5.2 Inclusion/Exclusion Criteria

Inclusion criteria: Patients aged 2-17 years old who undergo an appendectomy for acute, perforated appendicitis at CMHH. Diagnosis of perforated appendicitis is made intraoperatively

by the surgeon and is defined as the visualization of a gross defect in the appendiceal wall or the presence of intraperitoneal stool or a fecalith at the time of operation.

Exclusion criteria: 1) patients presenting with simple or gangrenous appendicitis, 2) patients with a history of iodine sensitivity, thyroid disease or renal disease, 3) patients undergoing interval or incidental appendectomy, and 4) pregnancy.

We do not anticipate pregnancy in our study population. Pregnant subjects and their fetuses may be placed at undue risk for the purposes of the study. Therefore, pregnant patients will be excluded from participating in the study.

Withdrawal: Prior to or after providing informed consent, patients may withdraw from the study at any point pre- or postoperatively by informing any of the care providers during the patient's hospital stay.

6.0 Study Procedures/Evaluations

6.1 Study Procedures

Randomization and allocation:

Enrollment will occur prior to the operation either in the emergency room, on the ward, or in the preoperative holding area. The randomization schema will be variable block randomization, and sequentially numbered, opaque, sealed envelopes will be used to blind allocation. Following consent, the sealed, opaque envelope will be attached to the patient's chart which accompanies the patient into the operating room. Only if the patient is found intraoperatively to have perforated appendicitis will the envelope be opened by the circulating nurse and the patient assigned to the control or intervention group. If a patient is determined to have simple or gangrenous appendicitis, the sealed envelope will remain unopened, and a research coordinator will retrieve it for re-use.

Standard Preoperative, Operative, and Postoperative Protocols

Upon patient admission to the hospital, the patient will be started on the preoperative appendicitis protocol that has been in place at CMHH since 2011. Briefly, this protocol entails immediate initiation of intravenous piperacillin-tazobactam or metronidazole/gentamicin for patients allergic to penicillin. The intravenous antibiotics are continued throughout the inpatient admission. Additionally, patients are fluid resuscitated and analgesia is provided.

A laparoscopic approach will be attempted for all patients; however, conversion from laparoscopy to an open technique will not result in exclusion from the trial. After carefully examining the peritoneal cavity and upon identifying the appendix, the surgeon will declare whether or not the patient has a perforated appendicitis (as defined previously). At that point, the circulating nurse will open the sealed envelope and group assignment will occur. Subsequently, once the surgeon has removed the appendix from the abdomen and ensured hemostasis, the surgeon will proceed to use the battery-powered, suction-irrigator device to irrigate primarily the right upper, right lower, and pelvic regions as these are the predominant locations for postoperative IAA formation [5]. If the patient is assigned to the intervention group, the nurse will create the dilute PVI irrigation by first removing 100ml of saline from a 1000ml bag and replacing it with 100ml of stock, 10% PVI (readily available in the operating room), thereby creating an irrigation solution with 1% PVI. Dilution of the PVI will occur while the surgeon completes the operation (removes the appendix). Once the appendix has been removed and hemostasis ensured, the surgeon will perform the irrigation with 10cc/kg (minimum 100ml and maximum 1000ml) of dilute PVI. The dose of PVI (10cc/kg) is based on previous studies [13,14] as well as consensus from our pediatric surgery team and is felt to be a conservative dose [14]. After completing the irrigation, the surgeon will suction out all intra-abdominal fluid into a suction canister and the amount will be recorded. Patients allocated to the control group will not undergo intra-abdominal irrigation.

All postoperative care will follow the standardized perforated appendicitis care pathway which includes continued intravenous antibiotics until they are discharged from the hospital. Standard discharge criteria for perforated appendicitis patients will comprise the following parameters: oral/axillary temperature < 100°F (oral) x 24hr, tolerating regular diet, pain relief with oral analgesics, ambulating with minimal assistance as age appropriate, normal white blood cell count

without bacteremia. Those patients who do not meet discharge criteria within seven days will undergo a computed tomography (CT). Patients diagnosed with an IAA on CT scan will receive an interventional radiology consultation and will undergo percutaneous drainage when deemed feasible by the interventional radiologist.

The same discharge criteria will apply for all patients. All patients will be scheduled for follow-up with a pediatric surgeon within one week of discharge. Those patients who are not able to attend the follow up appointment will be called and rescheduled. In the clinic, a post-appendectomy form (Appendix A) will be filled out by a pediatric surgeon who will document physical exam findings as well as any additional postoperative complications or visits to an emergency room (ER) or other healthcare facility as reported by the patient/parents. All patients will be called between 30-32 days postoperatively (in case postoperative day 30 falls on the weekend), and a form will be filled out that details any further complications or healthcare facility visits.

Postoperative Laboratory Testing & 6- and 12-month Follow Up

To verify the safety profile of PVI irrigation, at the time of intraoperative diagnosis of perforated appendicitis, the anesthesia provider will send a blood sample to the lab to measure baseline glucose, TSH, and T4 levels in 10 patients. Two additional samples will be sent at 24 hours and as needed at 72 hours postoperatively by the floor nurse. Pediatric endocrinology will follow these first 10 patients during their admissions and will provide therapeutic guidance in the unlikely event that symptomatic hypothyroidism occurs. Six and 12-month follow up with patients (via chart review and phone call) will take place to determine if any small bowel obstructions occur due to abdominal adhesions. Although rare, abdominal adhesions are a known entity after appendectomy and theoretically may be exacerbated by either normal saline or PVI irrigation.

7.0 Statistical Consideration

Providing both frequentist and Bayesian approaches has been shown to provide complementary interpretations [17]. Furthermore, while a frequentist analysis may result in a “negative” study, posterior probabilities based on a Bayesian approach may still be sufficient for clinicians to

implement an intervention despite an insignificant p-value or to recruit additional centers to participate in an ongoing study. There are several more reasons why performing a Bayesian analysis alongside a frequentist analysis may be beneficial, many of which are listed in a study by Wijeyesundera and colleagues [17]. Therefore, our study will include both frequentist and Bayesian analyses.

7.1 Study Outcome Measures

The primary outcome will be 30-day postoperative IAA rate. An IAA will be defined as an image-confirmed (ultrasound or CT) fluid collection deemed to be an IAA by a pediatric radiologist at CMHH. The imaging studies will be obtained for patients who undergo postoperative imaging at outside facilities and will be read by CMHH pediatric radiologists. The radiologists will remain blinded to the patient's intervention. Patients who are determined to have an IAA will be referred to interventional radiology for percutaneous drainage and will be restarted on intravenous antibiotics based on organism susceptibilities.

Secondary outcomes will include total hospital length of stay within 30 postoperative days and rates of readmissions and ER visits within 30 postoperative days. Total hospital length of stay will be the aggregate of all days in the hospital including any appendicitis-related readmissions within 30 postoperative days. Thirty-day ER visits and readmissions will also be determined through chart review, clinical encounters, and phone calls. Other adverse events that will be recorded will include abnormal thyroid function tests requiring endocrinology intervention immediately postoperatively and small bowel obstructions within one year after surgery.

A small outcomes adjudication committee will review a random sample of patient charts to verify the reported findings. Members of the committee will have no vested interest in the outcomes of the proposed study and will be blinded to treatment allocation.

The patient list will be generated when the pediatric surgery team informs the research coordinator that a patient with suspected appendicitis is being consented for an appendectomy. The patient MRN will be converted to a unique patient ID using a linking log that is accessible to the study coordinators. Electronic records from Children's Memorial Hermann Hospital and UT

professional building pediatric surgery clinic will be accessed. The data will be collected by the principle investigator and those listed in the IRB application. No patient identifiers will be collected. Data points to be abstracted from the electronic medical record or requested from the Memorial Hermann Hospital system will include:

1. Age
2. Race
3. Gender
4. Height
5. Weight
6. Admission date(s)
7. Admission time(s)
8. Admission location(s)
9. Discharge date(s)
10. Discharge time(s)
11. OR date(s)
12. Postoperative diagnosis
13. Operative procedures
14. Operative reports
15. Pathologic diagnosis
16. Laboratory results
17. Imaging type(s)
18. Imaging dates(s)
19. Imaging location(s)
20. Imaging results
21. Dates and causes of any readmissions
22. Medications administered, including antibiotics
23. Administration dates of medications
24. Side effects related to antibiotic administration
25. Dates of diet advancement
26. Date(s) of surgical site infections

27. Hospital costs (to be requested from the Memorial Hermann Hospital system)
- a. Direct and indirect costs associated with hospital stay

7.2 Sample Size Considerations

Using a frequentist approach, to demonstrate a clinically important decrease in IAA from 24% to 16% with 80% power and a two-tailed significance level of 0.05, a sample size of 784 patients (392 patients per group) would be required. Based on current practice (approximately 100 appendectomies are performed annually for perforated appendicitis) and an estimated consent rate of 50%, study enrollment would take approximately 15 years.

In anticipation of using a Bayesian approach, the CMHH pediatric surgeons have come to consensus that they would change the way they practice if a Bayesian analysis could determine with 75% confidence whether or not PVI is beneficial. Based on Monte-Carlo simulations using the prior probabilities described below, our pediatric surgeons are confident that a 2-year, pilot trial will provide sufficient power to guide future efforts (Appendix B).

7.3 Bayesian Prior Probabilities

A Bayesian prior represents the probability distribution that summarizes the beliefs about the treatment benefit prior to seeing study results. The prior is determined by taking into account existing evidence, expert knowledge and opinion, and defining clinically important outcomes. After thorough review of the current literature concerning intra-abdominal irrigation for perforated appendicitis (which are referenced in the Introduction) and discussion, the CMHH pediatric surgeons feel the following Bayesian priors are appropriate for analyzing the benefit of PVI in this trial (RR=relative risk, CI=confidence interval):

<u>Neutral:</u>	RR 1 (95%CI 0.5-1.6)	<u>Optimistic:</u>	RR 0.67 (95%CI 0.3-1.2)
	24% IAA (95%CI 13-37%)		16% IAA (95%CI 9-34%)

To determine the prior probability of treatment benefit for the control group (no irrigation), we will use three years of prospectively collected data from CMHH of patients who underwent the current protocol which is to not perform irrigation (n=325). Further strengthening this prior

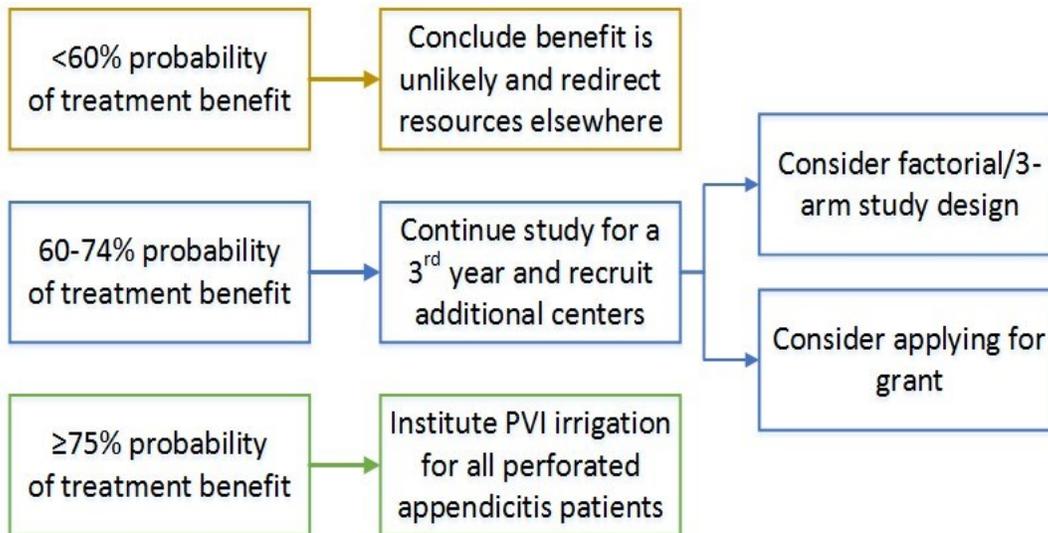
probability is the fact that similar results have been published by similar programs across the country [1,2]. The following prior will be used when analyzing the benefit of no irrigation (control group) during the trial: 24% IAA (95%CI 20-29%)

7.4 Participant Enrollment and Follow-Up

A multidisciplinary, post-appendectomy surveillance program developed by the Infection Control and Pediatric Surgery departments has been in place since 2011 and is tasked with prospective surveillance of all appendicitis patients. Through the joint efforts of both departments, all appendicitis patients are closely followed during the 30 days after discharge through electronic medical record review, wound culture review, and all SSI reporting among the Memorial Hermann Hospital affiliates (11 hospitals in the Houston metropolitan area). Each documented SSI is jointly reviewed by members of both departments during a monthly meeting.

7.5 *A Priori* Practice Algorithm

The CMHH pediatric surgeons have devised an *a priori* algorithm to guide their next steps in clinical practice based on the study results at the end of two years. The algorithm uses an optimistic prior probability of treatment success and takes into account the results of the Monte-Carlo simulations previously performed (Appendix B).



7.5 Analysis Plan

Demographics and baseline characteristics of each group will be clearly displayed in a table. Primary and secondary outcomes will be determined and compared for each group, including effect sizes and 95% CI. For binary outcomes, absolute and relative effect sizes will be determined. Bayesian probability models will also be performed to determine the likelihood and degree of treatment benefit. Chi-square, Fisher's exact, Student's t-test or Mann-Whitney U tests will be performed for categorical and continuous variables, respectively. Generalized linear models will be utilized to look at predictors of IAA, ER visits, readmissions, and LOS. The data will be analyzed based on their distribution.

A CONSORT flow diagram will be provided to clearly demonstrate the number of participants who were randomized, received the intended treatment, and were analyzed for the primary and secondary outcomes. The reasons for losses to each group will be documented; intention-to-treat (primary) and per-protocol (secondary) analyses will be performed.

Limitations

(1) Subjectivity of the primary outcome. An outcome such as IAA may be subjective due to variable definitions or interpretations. However, we utilized a standardized definition that is utilized, endorsed, and has been validated by other pediatric surgeons [18]. In addition, trained clinicians blinded to the allocation will make the assessments.

(2) Failure to blind the treating clinicians. Clinicians making treatment decisions may not be blinded to the intervention if they were present during the operation. However, postoperative protocols are in place to help minimize differential treatment based on treatment allocation. Additionally, the patients, radiologists, and data analysts will be blinded. Research coordinators will keep a separate spreadsheet to keep track of group assignment.

(3) Generalizability. This study will be performed on pediatric patients at a tertiary care academic center. The applicability of these results to other clinical settings may be limited. If this

study demonstrates safety and efficacy, other institutions will be recruited for a larger, multicenter trial.

7.7 Interim Analysis

Six months after the first patient is enrolled, an interim analysis will be conducted by an independent Data & Safety Monitoring Board to ensure there are no increased harms of PVI and that ongoing study participation is not futile.

7.8 Data Safety and Monitoring Board (DSMB)

The DSMB will be composed of a general surgeon, pediatric endocrinologist, infectious disease physician, statistician, and an academic surgeon with clinical trial experience.

Harms will entail but not be limited to: abnormal thyroid tests requiring endocrinology intervention or adhesive small bowel obstruction requiring readmission or surgery. There are no other anticipated harms imposed by PVI irrigation; however, any unexpected harms that arise will be included in the interim and final analyses. At the time of the interim analysis, if the probability of increased harms is >75% or the probability that PVI is beneficial is <10%, the study will be stopped and existing data will be reported.

8.0 Subject Confidentiality

Patient data will be entered into a secure, UT-Houston REDCap database [19] by the study coordinators. Only study investigators approved by the Institutional Review Board to participate in the study will have access to the REDCap data. Upon completion of the study, the REDCap database will be permanently deleted.

9.0 Informed Consent Process

Consent will be obtained from each participant prior to surgery after verification that all inclusion and exclusion criteria have been met. Patients will have the consent read to them by one of the coordinators and all questions will be answered. Minors will also be assented for the study. Subjects who speak languages other than English will be communicated with using an official interpreter via the Hermann translator line. This will allow the research team the

opportunity to discuss the consent, answer and questions and discuss the protocol with the assistance of a certified interpreter. All patients willing to be enrolled in the study will receive a signed copy of the consent form.

A Waiver of Consent will be requested for eligible study participants unable to provide assent or parents/guardians who refuse to sign an informed consent for the following reasons:

- Emergent intervention requiring medical sedation, incapacitation, and/or endotracheal intubation (i.e. septic shock, cardiopulmonary resuscitation)
- Auditory, visual, or mental impairment and/or learning disability
- Parent or guardian preference - refusal or declination to permit child to provide assent (i.e. extreme fatigue, weakness, lethargy)

10.0 Differences, Costs, and Funding

Currently, each arm of the study (PVI or no irrigation) has been deemed to be safe and is utilized commonly by some surgeons in some settings as the standard of care. The unique portion of the intervention is simply randomizing all of the interventions in a systematic fashion rather than in an arbitrary fashion (current practice).

We do not feel that any of the interventions or follow-ups represent a cost to the patient or healthcare system above current practice.

Currently, we are seeking funding to support this trial. However, without an IRB number and approved IRB, many funding sources are not available. We anticipate seeking funding from intra- and extra-mural grants.

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Appendix A: Pediatric Appendicitis, Standardized Clinical Follow-up Form

**Appendicitis Surgical Site Infection
Evaluation Form**

14 day 30 day

6/19/14

Date of Clinic visit: 06/09/14

Date of Discharge: 05/22/14

Was there an in-patient post-operative intra-abdominal infection YES NO

Wound evaluations: (check all that apply)

Site	No infection	Cellulitis	Pus	Stitch abscess
Right lower quadrant	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Umbilical port	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Suprapubic	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Left lower quadrant port	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Treatments: (check all that apply)

- None
- Opened wound (culture all open wounds, not skin)
- Oral antibiotics
 - 1st line (without history of MRSA)
 - Cephalexin (Keflex) 25 mg/kg/dose q 12 hours (max dose 4 g/day) for 10 days
 - Dispensed: 100mg/ml, 125mg/5ml, Tabs 500 or 1 gm, Caps 250 or 500 mg
 - 2nd line (with history of MRSA)
 - Clindamycin 10 mg/kg/dose q 8 hours (max dose 1.8g/day) for 10 days
 - Dispensed: 75 mg/5ml, Caps 75mg, 150 mg, 300mg
- Admitted from clinic

Comments: (Examples: Was infection treated by pediatrician? Was admitted to another hospital?)

Appendix B: Monte-Carlo simulations

Scenario 1:

- Sample size: n=100 (50/group)
 - True IAA rate (no irrigation): 24% (20-29%)
 - True IAA rate (PVI): 16% (95%CI 9-34%), RR 0.67 (95%CI: 0.3-1.2)
 - 75% posterior probability the RR<1
 - Optimistic prior: RR 0.67 (95% CI: 0.3-1.2)
- **89% power**

Scenario 2:

- Sample size: n=200 (100/group)
 - True IAA rate (no irrigation): 24% (20-29%)
 - True IAA rate (PVI): 16% (95%CI 9-34%), RR 0.67 (95%CI: 0.3-1.2)
 - 75% posterior probability the RR<1
 - Optimistic prior: RR 0.67 (95% CI: 0.3-1.2)
- **94% power**

Scenario 3:

- Sample size: n=100 (50/group)
 - True IAA rate (no irrigation): 24% (20-29%)
 - True IAA rate (PVI): 16% (95%CI 9-34%), RR 0.67 (95%CI: 0.3-1.2)
 - 75% posterior probability the RR<1
 - Neutral prior: RR 1 (95% CI: 0.5-1.6)
- **64% power**