Skin Antisepsis Prior to Surgical Fixation of Open Extremity Fractures

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Skin Antisepsis Prior to Surgical Fixation of Open Extremity Fractures: A Combined Analysis of Two Randomized Controlled Trials

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Thesis Abstract

Open fractures are devastating injuries that lead to significant morbidity and prolonged disability to a large number of patients worldwide. In addition to bony union, the prevention of infection is a primary goal in the surgical treatment of open fractures, and is an important factor in determining a positive outcome. In addition to preoperative antibiotics and tetanus prophylaxis, along with surgical irrigation and debridement, perioperative skin antisepsis is part of the standard of care for these injuries. Despite recent randomized trials investigating different primary active ingredients in these skin antiseptic agents, it remains unclear whether alcohol-based skin antiseptics outperform aqueous solutions.

This thesis comprises a combined analysis utilizing all open fracture participants from the PREP-IT trials, A-PREP and PREPARE. With these data, we were able to compare the risk of surgical site infection between alcohol-based and aqueous solutions, as well as examine specific subgroups including upper vs lower extremity open fractures as well as stratifying the fractures based on the severity of soft-tissue injury. The secondary outcome was to compare rates of unplanned reoperation up to 1-year following definitive fracture fixation.

We demonstrated that for a large and diverse population of open fracture patients, the use of an alcohol-based or aqueous solution did not have a significant effect on the risk of surgical site infection following surgery for an open fracture. Moreover, we showed that

there was also no significant difference in the risk of unplanned reoperation. These findings suggest that unlike in closed fractures as demonstrated by PREPARE, in open fractures the choice of surgical skin antiseptic agent has little impact on the risk of surgical site infection. This provides surgeons with the knowledge that either an alcohol-based or aqueous skin antiseptic solution can be used, and supports the use of iodine povacrylex in alcohol for all fractures given its proven effectiveness in the closed fracture population.

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Kyle

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Glossary of Abbreviations

A-PREP	Aqueous PREP
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CDC	Centers for Disease Control
CHG	Chlorhexidine Gluconate
CI	Confidence Interval
FLOW	Fluid Lavage of Open Wounds
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HiREB	Hamilton Integrated Research Ethics Board
HRQOL	Health Related Quality of Life
LMICs	Low and Middle Income Countries
MRSA	Methicillin-Resistant Staphylococcus Aureus
OR	Odds Ratio
SD	Standard Deviation
SSI	Surgical Site Infection

CHAPTER 1: BACKGROUND

The Burden of Open Fractures

Traumatic accidents represent a rapidly growing epidemic worldwide, and disproportionately affect those living in developing countries. It has been estimated that over 90% of the global injury burden occurs in low- and middle-income countries (LMICs),[1] and by 2030 it is expected that road traffic injuries alone will be the third largest contributor to the global burden of disease.[2] Open fractures, or fractures where the bone is exposed to the external environment due to soft tissue injury, represent a significant source of morbidity for patients worldwide and place patients at a high risk for infection and ongoing disability.[3–5]

Extremity fractures and the subsequent disability caused have the potential for profound socioeconomic and health related quality of life (HRQOL) impacts on those they affect. Major extremity fractures often lead to lost wages, financial distress, and extended time periods with patients unable to work.[6–9] Specifically for open fractures, patients are at a drastically elevated risk for developing an associated infection, with reported infection rates ranging from 5-20%, depending on location and severity.[5,10,11] For those open fractures with the most severe soft tissue injuries, that rate may be as high as 50%.[12–14]

With all surgically treated extremity fractures, and especially with open fractures, surgical site infection (SSI) is perhaps the most clinically relevant complication to avoid. Evidence would indicate that the presence of an SSI following surgery for an extremity

fracture results in a significantly decreased HRQL as well as typically at least two additional procedures to control the infection.[15] Lastly, due to the limited availability of timely surgery and expensive infection control measures in LMICs, reducing the risk of open fracture related infection has become a leading global health priority.[16,17]

The Current State of Open Fracture Care

Despite advances in surgical care over the past few decades, the primary goals with regards to the treatment of open fractures remain consistent. These are the prevention of infection via antibiotic prophylaxis, tetanus prophylaxis, and early surgical irrigation and debridement, as well as stabilization of fractures using either internal or external fixation.[18–20] However, there is also evidence to suggest that overall rates of infection following severe open fractures have remained high despite surgical advances. In a recent systematic review of over 11,000 open tibia fractures over four decades, it was demonstrated that type III fractures have infection rates of approximately 26-27%, and that these rates have remained similar over the past 40 years.[21]

While surgeons have known for years the importance of antibiotic prophylaxis for open fractures, more recently emphasis has been placed on simple cointerventions that may help reduce the overall bacterial load at the fracture site. These include the use of topical antibiotic powders placed in the wound as well as antibiotic beads, all aimed at increasing antibiotic delivery at the fracture site.[22–25] With the increased focus on simple

perioperative cointerventions, the current standard of care use of surgical skin antiseptic solutions has received newfound attention.

Surgical Skin Antisepsis

Given the emphasis placed on preventing infection in open fracture surgery, perioperative interventions such as preoperative skin antiseptic use are standard of care along with good sterile technique. The most common skin preparation solutions include either a chlorhexidine or iodophor-based active ingredient, and are delivered in an alcohol-based or aqueous solution. These available solutions take effect by killing bacteria on the skin and thereby reducing the quantity of native skin flora, and subsequently reducing the risk of SSI.[26–28] Iodophors, while being effective against most bacteria, are also thought to have broader coverage of viruses, mycobacteria, and some spores compared to chlorhexidine gluconate (CHG). CHG on the other hand is effective against most bacteria, and acts similarly by penetrating the cell wall of microorganisms.[29] However, chlorhexidine has no activity against bacterial spores.[30]

Furthermore, the choice of CHG or an iodophor active ingredient is further clouded by the presence of an alcohol-based or aqueous solution. The most commonly used iodine-based solution is the aqueous povidone-iodine, however there are concerns it may not function well in the presence of organic materials such as blood or pus, which can neutralize its bactericidal activity.[31] On the other hand, the commonly used CHG in alcohol solution does not have sufficient activity to eradicate some pathogens such as

methicillin-resistant *Staphylococcus aureus* (MRSA).[32] In a randomized trial of nearly 850 patients, CHG in alcohol was compared to povidone-iodine.[28] In this study the rate of SSI was significantly lower in the CHG-alcohol group (RR 0.59, 95%CI 0.41-0.85).[28] However, because this study compared an alcohol-based chlorhexidine solution to an aqueous solution (10% povidone-iodine), it is unclear whether the true effect is due to the is due to the efficacy of CHG compared to iodine, isopropyl alcohol compared to water, or even a synergistic effect of CHG in alcohol.[28]

Prior to the PREP-IT (A Program of Randomized trials to Evaluate Pre-operative antiseptic skin solutions In orthopaedic Trauma) trials, evidence on surgical skin antisepsis in extremity fracture surgery was limited, with most evidence guiding clinical practice being extrapolated from other disciplines. Generally speaking, the environment of open fracture surgery differs in many ways from that of other surgical settings. Traumatic wounds caused by fractures are often associated with significant soft tissue trauma, wound contamination, and disruption of local vascular supply. Additionally, extremity fracture surgery often includes tourniquet use, which can decrease blood flow to the area and may potentially increase infection risk. Lastly, internal or external fixation done to stabilize fractures introduces the presence of a metallic implant which can harbour bacteria. Altogether this creates a radically different environment than elective abdominal or gynecologic surgery, and authors recognize that studies performed on these patients may not apply to orthopaedic patients.[26]

Lastly, most literature investigating skin antisepsis prior to the PREP-IT trials utilized a 30-day endpoint for SSI.[26,27] While this is reasonable for most superficial SSIs, open fractures often present with deeper surgical site infections involving the muscle and/or bone well beyond 30 days post-injury. Furthermore, those deeper infections tend to be those that carry a greater risk of morbidity and are more likely to require reoperation. Evidence from previous trials in the management of open fractures, specifically from the FLOW trial, showed that almost half of the complications related to infection presented between 30 and 90 days post-injury.[5]

The PREP-IT Trials

Given the lack of clear evidence regarding surgical skin antisepsis in extremity fracture surgery, the PREP-IT trials were developed as a group of pragmatic, cluster-randomized trials to investigate these in both closed fracture and open fracture populations. For the work in this thesis, the trials involving only open fracture patients will be analyzed. These include the Aqueous PREP (A-PREP) trial, which investigated 4% chlorhexidine and 10% povidone-iodine aqueous solutions, and the PREPARE-Open trial, which compared 2% chlorhexidine in 70% isopropyl alcohol or 0.7% iodine povacrylex in 74% isopropyl alcohol.

The primary hypotheses from both trials above were that an iodophor solution would be more effective than chlorhexidine in preventing 90-day SSI and unplanned reoperations

within 1 year of surgery. These hypotheses were based on secondary multivariable analysis from the FLOW trial, which found that for 2,447 patients with open fractures, when compared to CHG solutions, iodophor-based skin antiseptic preparation solutions were potentially protective against complications (hazard ratio 0.88; 95% CI 0.69–1.12).[5] There are multiple reasons to suggest that iodophor solutions may be advantageous to chlorhexidine-based solutions. As mentioned previously, iodophor solutions have a potentially broader spectrum when it comes to antimicrobial acitivity.[29] Furthermore, the iodine povacrylex in alcohol solution has previously demonstrated that when it dries it forms a water-insoluble polymer-based film that prevents it from washing away.[26] This property would be especially advantageous in the surgical treatment of open fractures, as current recommendations for irrigation and debridement of open fractures include the use of anywhere from 3-9 L of irrigation fluid.[33]

At the conclusion of both trials, a total of over 3,000 open fracture patients had been included and were available for final analysis. In the A-PREP trial, a surgical site infection occurred in 59 patients (7.5%) in the povidone-iodine group and 58 patients (7.4%) in the chlorhexidine gluconate group (odds ratio 1.11; 95% CI 0.74 to 1.65; P=0.61). Similarly, in the PREPARE-Open trial, surgical-site infection occurred in 54 patients (6.5%) in the iodine group and in 60 patients (7.3%) in the chlorhexidine group (odds ratio 0.86; 95% CI 0.58 to 1.27; P=0.45). While neither trial was able to demonstrate superiority of an iodophor solution over CHG, questions remained about the

impact of the use of an alcohol-based solution, as well as any possible synergistic effects of the combination of alcohol with the active ingredient.

Alcohol-Based vs Aqueous Solutions

Given the findings of the A-PREP and PREPARE-Open trials, the question still remains regarding the overall effect of the skin preparation solution primary ingredient versus the use of an alcohol-based vs aqueous solution. This is especially compelling as pure alcohol solutions alone have been used for antisepsis historically, as it is thought to cause protein denaturation and membrane damage.[29,30]

Furthermore, there is recent evidence points towards the effect of the alcohol being a driving factor rather than the chlorhexidine or iodophor active ingredient.[34] Darouiche et al. showed the advantage of an alcohol-based CHG skin solution, yet when compared to an aqueous solution it was similarly unable to answer the question on the advantages of using an alcohol-based solution.[28] More recently, investigators from other areas have started to direct compare alcohol and aqueous solutions with the same active ingredient, though results from procedures such as venipuncture or minor skin excisions are quite unlikely to translate directly to open fracture surgery as outlined previously.[35,36]

Despite the proposed advantages of alcohol-based solutions, they do not come without some concerns specifically regarding open fractures. Alcohol-based solutions such as DuraPrep™ (3M, St. Paul, MN) often come with manufacturers recommendations that

the solution only be used on intact skin, given the risk of cytotoxicity of concentrated alcohol on open wounds. While PREPARE-Open specified the use of the antiseptic solutions to the manufacturer's recommendations for open fractures, the presence of open wounds during the period of preoperative skin antisepsis should be taken into consideration.

Purpose

The purpose of this thesis is to combine data from the methodologically rigorous PREP-IT trials to analyze the included patients as a single population. This will allow for comparison of alcohol-based and aqueous surgical skin preparation solutions to determine if there is a superior choice in skin preparation prior to fixation of open extremity fractures.

CHAPTER 2: Statistical Analysis Plan

Study Design

This study is designed as a combined secondary analysis utilizing the data from all open fracture patients from the PREP-IT trials (A-PREP and PREPARE) to compare alcohol-based and aqueous skin preparation solutions.[37] Combined this accounts for individual patient data from over 3000 patients, taken from two cluster-randomized trials which were conducted with the most rigorous methodology.

Objectives

The overall objective of this PREP-IT combined analysis is to compare alcohol-based and aqueous solutions for surgical skin preparation prior to operative treatment of open fractures.

Primary Objective and Hypothesis

To determine the effect of an alcohol-based skin preparation solution (2% chlorhexidine in 70% isopropyl alcohol or 0.7% iodine povacrylex in 74% isopropyl alcohol) versus an aqueous skin preparation solution (either 10% povidone-iodine or 4% chlorhexidine) in preventing surgical site infections. We hypothesize that the use of an alcohol-based antiseptic solution will be more effective in preventing surgical site infections (SSIs) than aqueous solutions.[38]

Secondary Objective and Hypothesis

To determine the effect of an alcohol-based skin preparation solution (2% chlorhexidine in 70% isopropyl alcohol or 0.7% iodine povacrylex in 74% isopropyl alcohol) versus an aqueous skin preparation solution (either 10% povidone-iodine or 4% chlorhexidine) in preventing unplanned fracture-related reoperations. We hypothesize that the use of an alcohol-based antiseptic solution will be more effective in preventing unplanned reoperations than aqueous solutions.

Subgroup Analyses

This combined analysis will include four subgroup analyses to determine the effects of alcohol-based versus aqueous skin antiseptic solutions on surgical site infection within these subgroups. The primary subgroups will be those treated with an antiseptic solution with the main ingredient of chlorhexidine versus iodine. In this way we can compare the effects on SSI of aqueous chlorhexidine versus chlorhexidine in alcohol and of aqueous iodine versus iodine povacrylex in alcohol. We hypothesize that in both subgroups, the alcohol-based solution will have a greater effect in preventing SSI.

The third and fourth subgroups will compare alcohol-based and aqueous solutions in important clinical subgroups, first by severity of the open fracture as defined by Gustilo and Anderson,[39] as well as by upper versus lower extremity fracture location. We hypothesize that the magnitude of the effect alcohol-based solutions when compared to aqueous solutions in preventing surgical site infection will be greater in Gustilo-Anderson

Type III open fractures versus Gustilo-Anderson Type I or II open fractures, as well as in lower extremity fractures versus upper extremity fractures.

Data Sources

Included patients in this combined analysis of two clinical trials were those patients with an open fracture of the appendicular skeleton treated with surgical fixation. Patients were included from both the A-PREP trial and the PREPARE-Open trial. Patients with incomplete data were excluded. Data will be obtained from the Surgery Methods Centre at McMaster University, the primary methods centre for the above trials, and will be verified by those at the methods centre. As both trials included the same length of follow-up for the participants, no adjustments will need to be made when pooling patients. Included studies had to be approved by local ethics committees. We considered whether to include other trials of alcohol-based and aqueous skin antiseptics in our combined analysis. As has been done in other combined analyses,[40] we chose to exclude additional smaller studies at higher risk of bias and instead focus on two large studies with more than ample sample size to address the question of interest.

Data Management

Data from the A-PREP and PREPARE-Open trials is managed by the Surgery Methods Centre at McMaster University. Data will be combined form the two trials to create an overall data set of all open fracture participants. We will include core demographic and outcome data from the two trials. As the two trials had the same endpoints, there will be

ease in combining the outcome data. The lead statistician will be responsible for combining the data, which will be coded in such a way for data from both trials to be integrated. Permission for use of the data was provided by the principal investigators.

Study Population

General Population

In both of the included studies, all patients who presented to a participating hospital with an open fracture over the age of 18 were screened for study participation. Patients were included if their open fracture was treated definitively with a surgical implant(s) (e.g., internal fixation, external fixation, or arthroplasty) and if they underwent formal surgical debridement within 72 hours of the injury. Excluded patients were those with fractures of the hand, those that received previous surgical debridement at a non-participating site, those with pre-existing chronic or acute infection at the fracture site, burns at the fracture site, or expected survival less than 90 days whether secondary to their injuries or a terminal pre-existing illness.

Participant Demographics, Fracture Characteristics, and Descriptions of Surgical Care

Participants will be described with respect to age, sex, body mass index (BMI), diabetes and smoking status, American Society of Anesthesiologists (ASA) classification, and Injury Severity Score (ISS). Fractures will be described with regards to anatomic location as well as severity according to the Gustilo-Anderson classification.[39] The method of wound closure will also be recorded. Categorical data will be summarized by counts with

percentages. Age will be summarized as a mean with standard deviation. We will report the Injury Severity Score as a median with an interquartile range. Body mass index (BMI) will be reported in kg/m^2 and subcategorized as underweight (BMI<18.5), normal weight (18.5–24.9), overweight (25–29.9), and obese (BMI>30). All reporting will be stratified by treatment groups. We will not statistically test for differences in baseline characteristics between treatment groups; however, the clinical importance of any imbalance will be noted.

Outcome Definitions

Primary Outcome

Our primary outcome is SSI, informed by the 2017 Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network reporting criteria.[41] Based on this definition, the surveillance period for superficial SSI ended 30 days after definitive fracture management surgery, while the surveillance period for deep/organ space SSI ended at 90 days. For those patients where multiple tissue levels were involved in the infection, the type of SSI was defined by the deepest tissue layer involved during the surveillance period. Thus, only one type of SSI was reported per participant. All reported SSIs were reviewed by a blinded adjudication committee. Given that some patients undergo more than one fracture operation due to an intentionally staged treatment plan (including multiple debridements, soft tissue coverage procedure, temporary external fixation, definitive fixation etc.), the 30- and 90-day postoperative periods will be relative to their definitive fracture management surgery.

Secondary Outcome

The secondary outcome is the occurrence of an unplanned fracture-related reoperation within 12 months of the surgery. This outcome is common and important to patients, as it encompasses both reoperation for infection or wound healing complications as well as reoperation for issues with bony healing, which can be related to an occult infection.[42] These include irrigation and debridement of open fracture wounds due to infection or wound healing issues, revision wound closure for dehiscence, soft-tissue coverage procedures for infected wounds, and surgery performed for nonunion or hardware failure. The blinded adjudication committee reviewed all reported reoperations.

Statistical Analysis

Descriptive Analyses

Baseline characteristics will be presented in a descriptive fashion to compare the two treatment groups (alcohol-based versus aqueous skin antiseptic). This will be represented in Table 1 in the final manuscript. Statistical testing on potential differences between groups will not be done however imbalances will be noted.

Primary and Secondary Outcomes

Groups will be compared with regards to the primary outcome on an intention-to-treat basis. We will report the number and percentage of patients who sustain the study outcome by treatment group. A mixed-effects regression model with a binomial

distribution will be used treating the open fracture participants from both A-PREP and PREPARE as a single cohort. In this way the analysis will be first conducted similar to that of a trial with a factorial design, with each individual participant being treated as though they have received two interventions, the first being an alcohol-based or aqueous skin prep solution and the second being an iodophor or chlorhexidine solution. While the primary goal is to determine the effectiveness of alcohol-based vs aqueous solutions, this analysis will also be aimed at determining if there is any interaction between the solution type (alcohol vs aqueous) and the primary active ingredient (chlorhexidine vs iodophor). If there is no independent interaction between the two treatments, this will be reported and the analysis will be conducted simply comparing alcohol-based and aqueous solutions. The regression models will be utilized to produce treatment effect estimates presented as odds ratios with 95% confidence intervals.

The models will also include prespecified covariates prognostic of infection or reoperation as fixed effects. These include fracture location, severity of the open fracture, and severity of wound contamination.[43] The same covariates will be used for primary and secondary outcomes. Lastly, to account for any potential confounding from cluster variability, the cluster will be included as a random intercept.

Subgroup Analyses

For the subgroup analyses, we will complete the above analyses for the primary and secondary outcomes on the pre-specified subgroups of patients. These include those with

lower extremity fractures versus upper extremity fractures, those with type I and II open fractures compared to type II open fractures, and those treated with a chlorhexidine - based vs iodophor skin preparation solution. Subgroup analyses will be reported in accordance with best practices and recent guidelines for subgroup analyses.[44–48]

Statistical Software

The statistical analyses will be performed with SAS, version 9.4 (SAS Institute, Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria).

Ethics Statement

All PREP-IT studies received ethics board approval from both the Hamilton Integrated Research Ethics Board (HiREB) as well as the ethics boards of the individual centres who participated in the trials.

CHAPTER 3: Alcohol-Based Versus Aqueous Skin Antisepsis Before Surgical Fixation of Open Fractures: A PREP-IT Combined Analysis

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Abstract

Purpose: Skin antisepsis remains a vital component in prophylaxis against surgical site infection (SSI), however for open fractures it is unclear whether alcohol-based or aqueous solutions should be preferred. The purpose of this study was to compare the use of alcohol-based and aqueous skin antisepsis solutions, using data from the PREP-IT trials (A-PREP and PREPARE), on the risk of SSI following surgery for an open fracture.

Methods: Individual patient data from two cluster-randomized, crossover clinical trials were combined to create one data set of patients undergoing surgery for an open fracture. A regression model was used to analyze the effects of an alcohol-based or aqueous solution, as well as for potential interaction of chlorhexidine or iodine as the primary agent. The primary outcome was SSI within 90 days, and the secondary outcome was unplanned fracture-related reoperation within one year.

Results: A total of 3,338 patients undergoing surgery for an open fracture were included in the final analysis, with 1700 receiving an alcohol-based solution and 1638 receiving an aqueous solution. Overall, the use of an alcohol-based skin antiseptic solution did not reduce the risk of SSI at 90 days (Odds Ratio [OR] 0.99, 95% CI 0.66-1.48, P=0.95), or the risk of unplanned reoperation at 1 year (OR 0.98, 95% CI 0.75-1.28, P=0.88). Planned subgroup analysis also found no significant difference in risk of SSI or unplanned reoperation when patients were stratified by Gustilo-Anderson type, fracture location, or primary ingredient of the skin prep solution (chlorhexidine vs. iodophor).

Conclusion: This analysis found that there was no evidence of any difference in the risk of SSI or reoperation when comparing alcohol-based and aqueous skin preparation solutions. Furthermore, while this analysis demonstrated no harm to using an alcohol-based solution for open fractures, the PREPARE trial found that for closed fractures skin preparation with 0.7% iodine povacrylex in 74% isopropyl alcohol had a reduced risk of SSI. Given these findings, surgeons should consider treating all fracture patients with 0.7% iodine povacrylex in 74% isopropyl alcohol to streamline policy with a single skin antiseptic for all fractures.

Key Messages:

- While the PREP-IT trials found no difference between groups based on the skin antiseptic primary active ingredient, alcohol-based and aqueous solutions were not directly compared
- Results of this secondary analysis found no difference in the risk of surgical site infection when open fractures were treated with an alcohol-based or aqueous skin antiseptic solution
- Given the advantages of iodine povacrylex in alcohol for closed fractures, as well as the equivocal findings for open fractures, surgeons should consider treating all fracture patients with iodine povacrylex in isopropyl alcohol to streamline policy

Background

Open fractures of the extremities are debilitating injuries and lead to a significant amount of disability for those they affect. Furthermore, they disproportionately affect those living in the developing world due to the public health crisis of traumatic accidents.[2] These injuries are especially troublesome due to the high risk of infection that accompanies these injuries.[5] Surgical management of open fractures consists of thorough irrigation and debridement in the operating room, systemic antibiotic prophylaxis and surgical stabilization of the fracture.[19,20,49] Part of routine perioperative operating room practices also include strict sterile technique and preoperative skin preparation with an antiseptic solution.

While skin antisepsis is universally recommended in various clinical practice guidelines, they often recognize a lack of consensus on the active ingredient, chlorhexidine gluconate (CHG) versus an iodophor.[50–53] Furthermore, there is additional uncertainty as to the use of either an alcohol-based or aqueous skin antiseptic, though many guidelines suggest the use of an alcohol based solution. [50–53] While there is literature examining the use of surgical skin antiseptics, this very rarely includes patients with open fractures, who have their own unique set of risk factors for infection. These include soft tissue trauma, wound contamination, and disruption of local vascular supply, along with use of metallic implants for internal or external fixation of fractures.

Given the relative dearth of literature on surgical skin antisepsis in extremity fracture patients, the PREP-IT trials were designed to compare skin antiseptics on the basis of their active ingredient, with Aqueous PREP comparing aqueous CHG vs an iodophor, and PREPARE comparing CHG in alcohol to iodine povacrylex in alcohol.[10,54] While for open fracture patients these studies found no significant difference with regards to SSI, there was no direct comparison between alcohol-based and aqueous solutions.

To determine the effects of an alcohol-based vs aqueous skin preparation antiseptic solution, a combined analysis was designed to pool data from two large, cluster-randomized controlled trials investigating surgical skin preparation prior to open fracture fixation. The purpose of this study was to compare the effectiveness of alcohol-based and aqueous solutions with regards to incisional or deep SSI as well as unplanned fracture related reoperation. Secondarily, we sought to examine for any potential interaction between the primary active ingredient (chlorhexidine vs iodophor) along with the solution type.

Methods

Study Design

This study was a secondary analysis of the PREP-IT trials, with a focus on the open fracture population. This was designed as a combined analysis of two large trials, synthesizing internal data from the both A-PREP and PREPARE-Open.

Eligibility Criteria

To be eligible for this combined analysis, studies had to be randomized controlled trials investigating the use of various skin antiseptic solutions prior to surgical management of open fractures. We chose to only include the two large cluster-randomized trials conducted as part of PREP-IT for analysis. The inclusion criteria were: (1) randomized controlled trials, (2) studies investigating an alcohol-based or aqueous skin antiseptic, (3) skin antisepsis prior to open fracture surgery, and (4) primary outcome of surgical site infection. Exclusion criteria included: (1) non-randomized studies, (2) pilot studies, (3) studies investigating skin antisepsis prior to surgical procedures other than fixation of open fractures, and (4) ongoing trials.

Study Identification and Selection

Two cluster-randomized trials were included in the final analysis, the Aqueous-PREP (A-PREP) and Pragmatic Randomized Trial Evaluating Preoperative Alcohol Skin Solutions in Fractured Extremities (PREPARE) trials.[10,54] Given that the PREPARE trial enrolled both patients with open and closed fractures, only the open fracture population from this

study was included. These two large trials were ideal for combining data given the similarities in recruitment, patient eligibility, and outcome assessment.

Data Collection

Individual patient data from the two included studies were available via the Surgery Methods Centre at McMaster University. This functioned as the central coordination site for the two trials and as such had access to the raw data from both trials that had been meticulously checked. Primary investigators from both trials gave permission for the individual-level data from both trials to be used in this project. All data from A-PREP and data from open fracture participants in PREPARE were included.

Data from the two included trials which were utilized included patient demographics including age, sex, and BMI, as well as prognostic factors including location of fracture, severity of open fracture, and degree of wound contamination. Additionally, data was collected on the primary and secondary outcomes for alcohol-based vs aqueous solutions and was stratified for predefined subgroups. Data was analyzed in duplicate by two independent statisticians (SB, NO) and results were compared to ensure accuracy of the models.

Primary and Secondary Outcomes

Full descriptions of the primary and secondary outcomes are available in the statistical analysis plan. In brief, the primary outcome is SSI, informed by the 2017 Centers for

Disease Control and Prevention's (CDC) National Healthcare Safety Network reporting criteria.[41] Based on this definition, the surveillance period for superficial SSI ended 30 days after definitive fracture management surgery, while the surveillance period for deep/organ space SSI ended at 90 days.

The secondary outcome is the occurrence of an unplanned fracture-related reoperation within 12 months of the surgery. This outcome encompasses both reoperation for infection or wound healing complications, as well as reoperation for issues with bony healing, which can be related to an occult infection.[42] These include irrigation and debridement of open fracture wounds due to infection or wound healing issues, revision wound closure for dehiscence, soft-tissue coverage procedures for infected wounds, and surgery performed for nonunion or hardware failure.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework will be used to judge the quality of the evidence for the primary and secondary outcomes.[55]

Subgroup Analysis

Subgroup analyses were performed comparing alcohol-based and aqueous solutions for pre-defined subsets of patients as laid out in the statistical analysis plan. These include those with lower extremity fractures versus upper extremity fractures, those with type I and II open fractures compared to type II open fractures, and those treated with a

chlorhexidine -based vs iodophor skin preparation solution. Subgroup analyses will be reported in accordance with best practices and recent guidelines for subgroup analyses.[44–48]

Statistical Analysis

Baseline characteristics will be presented in a descriptive fashion to compare the two treatment groups (alcohol-based versus aqueous skin antiseptic).

Groups will be compared with regards to the primary outcome on an intention-to-treat basis. We will report the number and percentage of patients who sustain the study outcome by treatment group. A mixed-effects regression model with a binomial distribution will be used treating the open fracture participants from both A-PREP and PREPARE as a single cohort. The model first assessed for any independent interaction between the primary active ingredient and solution type. This was not significant for the primary outcome (P=0.38) and so alcohol-based and aqueous solutions were simply compared. The regression models will be utilized to produce treatment effect estimates presented as odds ratios with 95% confidence intervals.

The models will also include prespecified covariates prognostic of infection or reoperation as fixed effects. These include fracture location, severity of the open fracture, and severity of wound contamination.[43] The same covariates will be used for primary and secondary outcomes. To account for any potential confounding from cluster variability,

the cluster will be included as a random intercept. R was used for all analyses (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

There was a total of 3,338 patients included in the combined population (Table 1). This included 1,700 patients who received skin antisepsis with an alcohol-based solution and 1,638 who received an aqueous solution. The majority of these patients were male (62.6%) and the mean age was 44.7 years (SD 18.1).

Data on the fractures and their management was available on 3,627 patients (Table 2). Most patients had Gustilo-Anderson type IIIA fractures (39.0%) followed closely by type II fractures (32.6%). The large majority were lower extremity or pelvic fractures (73.9%) and most had non or minimal contamination (63.0%).

Study Risk of Bias Assessment

The two included trials in this combined analysis were evaluated using the Cochrane risk of bias tool for cluster-randomized trials.[56,57] The overall risk of bias for both studies was deemed to be low. Of the five domains, the risk of bias was deemed low for the randomization process, missing outcome data, outcome measurement, and the selection of the reported result. There were some concerns regarding deviation from the intended intervention as there was crossover between groups in both studies, however the reported frequencies were low.

Primary Outcome

There was a total of 3,222 patients evaluated for the primary outcome of surgical site infection. Surgical site infection occurred in 114 of 1651 (6.9%) patients in the alcohol-based solution group and in 117 of 1,571 (7.1%) in the aqueous solution group (Table 3). This resulted in an odds ratio of 0.99 (95% CI 0.66-1.48, P=0.95). The GRADE quality of evidence for the primary outcome was moderate, being rated down for imprecision due to the wide confidence interval.[58]

Secondary Outcome

There was a total of 3,041 patients evaluated for the secondary outcome of unplanned reoperation within one year. Reoperation occurred in 240 of 1569 (15.3%) patients in the alcohol-based solution group and in 233 of 1,472 (15.8%) in the aqueous solution group (Table 3). This resulted in an odds ratio of 0.98 (95% CI 0.75-1.28, P=0.88). The GRADE quality of evidence for the secondary outcome was moderate, once again being rated down for imprecision.

Subgroup Analyses

The key subgroups evaluated were those based on the active ingredient of the solution, an iodophor or chlorhexidine. When examining these subgroups, there was no significant difference with regards to SSI for either subgroup when comparing alcohol-based and aqueous solutions (Table 4). Furthermore, there were no differences in unplanned reoperations for those subgroups when comparing the alcohol-based and aqueous solutions.

Additional subgroups evaluated as prespecified included location of the fracture (upper or lower extremity), as well as severity of the open fracture (Gustilo type I or II vs Gustilo type III). Neither of these subgroups substantially modified the treatment effect of an alcohol-based solution as compared to an aqueous solution (Table 4).

Discussion

Summary of Findings

In a combined population of over 3000 patients with open fractures, the risk of surgical site infection did not differ significantly whether patients were treated with an alcohol-based or aqueous skin antiseptic solution prior to surgical fixation. Moreover, no difference was seen in the secondary outcome of unplanned reoperation at 1 year. Lastly, no significant effect modification was seen for the subgroups based on primary active ingredient, fracture location, or the severity of the open fracture.

Relation to Current Evidence

The key finding of the PREP-IT trials came out of the closed fracture population in the PREPARE trial. Specifically, this trial found that for patients with closed fractures, SSI occurred in 2.4% of patients in the iodine group and 3.3% of patients in the chlorhexidine group, for an odds ratio of 0.74 (95% CI 0.55-1.00, P=0.049).[54] Despite this significant finding, there was still no consensus on the ideal surgical skin preparation solution for open fractures. Both the open fracture population in PREPARE as well as A- showed no significant difference in the risk of SSI. However, these trials did not directly compare an alcohol-based and aqueous skin preparation solution.

The findings of this study support that for open fractures, no specific approach to surgical skin preparation has been shown to be advantageous. One potential reason for this continued lack of a significant treatment effect is that open fractures are irrigated with

typically 3 to 9 litres of normal saline during the initial irrigation and debridement phase of the surgery. This usually occurs within minutes of surgical skin preparation and may result in much of the surgical skin preparation solution being washed away in the very early stages of the surgery. Secondly, open fractures are unique in that the protective soft tissue envelope of the skin has already been broken prior to skin incision, and so the soft tissues deep to the skin have already been exposed to bacteria in the environment, and often significant levels of contamination. This also means that by the time the patient is brought to the operating room hours later, bacteria have already seeded the deep tissues and may already be involved in early biofilm formation. It is plausible that given this, the antiseptic solution applied to the skin has a relatively minor role in the prevention of infection, such that the risk of infection is not measurably altered by the skin antiseptic choice. There is evidence that supports the use of alcohol-based skin antiseptics, such as a 2015 Cochrane Review which suggested that alcohol-containing products had the highest probability of being effective.[59] However, this is for clean procedures, for which the expected rate of surgical site infection is ~2%.[60] These procedures differ significantly from open fracture surgeries, where the deep soft tissues have already been exposed to skin flora well before skin antisepsis in the operating room.

Strengths

The primary strength of this PREP-IT secondary analysis was its ability to pool individual patients from two large randomized trials on open fracture management, in an area that has a paucity of literature. Both PREPARE and A-PREP came out of the same program of

randomized trials to evaluate preoperative skin antisepsis, known as PREP-IT. These trials were as such governed by a master protocol approach,[61] which lent several advantages to this combined analysis. Generally speaking, master protocols allow for a single overarching protocol to evaluate multiple potential hypotheses with the goal of improving efficiency.[62] In this case, the fact that both included trials came from the same master protocol allowed for reduced bias given the similarities in patient recruitment, inclusion and exclusion criteria, the definitions of outcomes, and the way outcomes were assessed. This allowed for streamlined pooled analysis of the two trials, with minimal concern for differences between outcome assessment in the individual trials. Additionally, a majority of sites that recruited patients for one study actually were involved in both studies, creating internal validity. Overall, this resulted in minimal heterogeneity between included studies with regards to patient population, outcome definitions, and outcome assessment. Furthermore, this study compared the two main classes of surgical skin antiseptics and is widely applicable to clinical practice for anyone treating open fractures.

Limitations

This study was not without its limitations, the most obvious being the inclusion of only two studies in this combined analysis. While this is only a small number of studies, given that the studies were quite large there was still over 3000 patients included in the final analysis. Additionally, some of the other concerns raised with few studies included such as the concern about generalizability are mitigated as both studies recruited patients from over 20 hospitals in the United States and Canada. Nevertheless, the patient population

and local patterns of bacterial flora as well as bacterial resistance may make these findings less applicable to those outside of North America.

Recommendations

This secondary analysis, along with both PREPARE and A-PREP, supports that for open fractures, there is no one clear skin preparation strategy that results in a significant reduction in the risk of SSI. While the evidence is clear in supporting the use of iodine povacrylex in alcohol for surgery on closed fractures, there is still uncertainty regarding the optimal skin preparation for open fracture surgery. It is recognized that the use of an alcohol-based skin antiseptic is potentially problematic in open fractures, as manufacturers recommend that the alcohol-based skin antiseptics be kept out of open wounds. While PREP-IT investigators instructed sites to use products in accordance with manufacturers recommendations, it is unlikely that alcohol based skin antiseptics would not be applied to open wounds, some of which can be complex and very deep in open fractures. Despite this, no deleterious effects were seen with the use of alcohol-based solutions in open fractures. Taking all of the evidence into account, this would support the use of iodine povacrylex in alcohol as the primary skin preparation solution for all fracture surgery, though potential patient allergies to an ingredient in the solution will still require hospitals to have alternatives available.

Conclusions

This analysis found that there was no evidence of any difference in the risk of SSI or reoperation when comparing aqueous and alcohol-based skin preparation solutions. Furthermore, while this analysis demonstrated no harm to using an alcohol-based solution for open fractures, the PREPARE trial found that for closed fractures skin preparation with 0.7% iodine povacrylex in 74% isopropyl alcohol had a reduced risk of SSI. Given these findings, surgeons should consider treating all fracture patients with 0.7% iodine povacrylex in 74% isopropyl alcohol to streamline policy with a single skin antiseptic for all fractures.

Table 1. Characteristics of the Participants at Baseline

Characteristic	Alcohol-Based Solution (n=1700)	Aqueous Solution (n=1638)
Age, years, mean (SD)	44.6 (18.2)	44.9 (18.1)
Sex, n (%)		
Female	621 (36.5)	627 (38.3)
Male	1079 (63.5)	1009 (61.6)
Prefer not to answer	0 (0.0)	2 (<1.0)
Race, n (%)		
White	1173 (69.0)	1289 (78.7)
Black	441 (25.9)	261 (15.9)
Asian	39 (2.3)	30 (1.8)
Prefer not to answer	15 (<1.0)	18 (1.1)
Indigenous	21 (1.2)	18 (1.1)
Central or South American	3 (<1.0)	16 (1.0)
Multiracial	6 (<1.0)	5 (<1.0)
Native Hawaiian or Pacific Islander	2 (<1.0)	1 (<1.0)
Body mass index, kg/m^2, n (%)		
Underweight (BMI < 18.5)	25 (1.5)	19 (1.2)
Normal weight (18.5 – 24.9)	502 (29.5)	443 (27.0)
Overweight (25 – 29.9)	573 (33.7)	518 (31.6)
Obese (BMI > 30)	600 (35.3)	658 (40.2)
Diabetes of any type, n (%)	144 (8.5)	170 (10.4)
Current smoker, n (%)	571 (33.6)	567 (34.6)
Injury severity score, mean (SD)	13.2 (8.3)	13.1 (9.3)
American Society of Anesthesiologist Physical Score, n (%)		
Class I or II	903 (53.1)	859 (52.4)
Class III or higher	797 (46.9)	779 (47.6)
Number of included closed fractures per participant, n (%)		
One	1553 (91.4)	1528 (93.3)
Two	130 (7.6)	95 (5.8)
Three	17 (1.0)	15 (<1.0)

Table 2. Fracture Characteristics and Management

Characteristic	Alcohol-Based Solution (n=1864 fractures)	Aqueous Solution (n=1763 fractures)
Severity of open fracture, n (%)		
Gustilo-Anderson type I	432 (23.2)	412 (23.4)
Gustilo-Anderson type II	633 (34)	548 (31.1)
Gustilo-Anderson type IIIA	722 (38.7)	692 (39.3)
Gustilo-Anderson type IIIB or IIIC	77 (4.1)	111 (6.3)
Location of fracture, n (%)		
Lower extremity or pelvis	1359 (72.9)	1320 (74.9)
Upper extremity	505 (27.1)	443 (25.1)
Wound contamination, n (%)		
None or minimal contamination	1149 (61.6)	1137 (64.5)
Surface contamination	548 (29.4)	456 (25.9)
Contaminant embedded in bone or deep soft tissue	167 (9.0)	170 (9.6)
Temporary fracture stabilization, n (%)	349 (18.7)	400 (22.7)
Number of planned surgeries, n (%) 1 2 3 4 5 or more	 1351 (72.5) 374 (20.1) 80 (4.3) 22 (1.2) 37 (2.0)	 1152 (65.3) 387 (22.0) 119 (6.7) 41 (2.3) 64 (3.6)
Duration of antibiotic administration (days), median (IQR)*	3.0 (2.0-3.7)	3.0 (2.0-4.0)
Closure method, n (%)†		
Primary wound closure	1714 (92)	1558 (88.4)
No closure attempted/secondary wound healing	31 (1.7)	34 (1.9)
Skin graft	55 (3.0)	65 (3.7)
Local flap	32 (1.7)	48 (2.7)
Free flap	32 (1.7)	58 (3.3)

* Duration based on receiving at least one antibiotic dose in a calendar day.

† More than one type of closure method may have been performed during surgery, but only the most complex method of closure is reported in the table using the following the hierarchy: 1) free flap, 2) local flap, 3) skin graft, 4) no closure attempted/secondary wound healing, 5) primary wound closure

Table 3. Study Outcomes

	Alcohol-Based Solution (n=1700) number (%)	**Aqueous Solution (n=1638) number (%)**	**Odds Ratio (95% Confidence Interval)**	**P Value**
Primary Outcome	**n=1651**	**n=1571**		
Surgical site infection	114 (6.9)	117 (7.1)	0.99 (0.66, 1.48)	0.95
Secondary Outcome	**n=1569**	**n=1472**		
Unplanned reoperation by 365 days	240 (15.3)	233 (15.8)	0.98 (0.75, 1.28)	0.88

Table 4: Subgroup Analysis – Study Outcomes

	Alcohol-Based Solution (n=1700)	Aqueous Solution (n=1638)	Odds Ratio (95% Confidence Interval)	Interaction p-value
Primary Outcome - Surgical site infection				
Severity of the Open Fracture				
Gustilo-Anderson type I or II	42/947	34/855	0.98 (0.55, 1.75)	0.63
Gustilo-Anderson type III	72/704	83/716	1.01 (0.63, 1.62)	
Location of the Open Fracture				
Upper extremity	9/432	11/388	0.72 (0.29, 1.77)	0.48
Lower extremity	105/1219	106/1183	0.99 (0.64, 1.54)	
Solution Primary Active Ingredient				
Chlorhexidine	60/826	60/784	1.16 (0.68, 1.97)	0.60
Iodophor	54/825	54/787	0.87 (0.55, 1.39)	
Secondary Outcome - Unplanned Reoperation Within One Year				
Severity of the Open Fracture				
Gustilo-Anderson type I or II	94/902	76/803	1.07 (0.76, 1.52)	0.68
Gustilo-Anderson type III	146/667	157/669	0.94 (0.67, 1.34)	
Location of the Open Fracture				
Upper extremity	35/411	33/358	0.95 (0.53, 1.69)	0.65
Lower extremity	205/1158	200/1114	0.97 (0.72, 1.30)	
Solution Primary Active Ingredient				
Chlorhexidine	114/785	115/738	0.97 (0.68, 1.37)	0.52
Iodophor	126/784	118/734	0.99 (0.70, 1.40)	

CHAPTER 4: Discussion and Conclusions

Thesis Summary

This thesis used the PREPARE and A-PREP trials to create a pooled patient population of over 3200 patients with open fractures, with the goal of comparing alcohol-based and aqueous surgical skin antiseptic solution. While both trials compared the active ingredients of chlorhexidine gluconate and an iodophor, there was no direct comparison between alcohol-based and aqueous solutions. By combining patients from both trials in a a combined approach, we were able to compare these two groups to determine any difference in the risk for surgical site infection.

The primary findings of this analysis were that in a combined population of over 3000 patients with open fractures, the risk of surgical site infection did not differ significantly whether patients were treated with an alcohol-based or aqueous skin antiseptic solution prior to surgical fixation. Additionally, no significant differences were seen for any of the prespecified subgroups based on primary active ingredient, fracture location, or severity of the open fracture.

Clinical Implications and Recommendations

The major findings of the two PREP-IT trials were that for closed fractures, iodine povacrylex in alcohol outperformed CHG in alcohol when it came to reducing the risk of surgical site infection. However, both A-PREP and PREPARE failed to find a difference

when comparing an iodophor and chlorhexidine based solution for open fractures, whether that be in the form of an alcohol-based or aqueous solution. This combined analysis of two trials was able to compare the alcohol and aqueous solutions directly, irrespective of the primary active ingredient, and also found no significant difference with regards to the risk of surgical site infection. It further supports the notion that for open fractures, likely due to the nature of these injuries and their surgical treatment, the use of a specific surgical skin antiseptic has such a small effect on overall infection risk that even with very large trials we are unlikely to see a difference. However, this study also showed no harmful effects of the use of alcohol-based skin antisepsis in the presence of open wounds, suggesting that combined with the known evidence for the benefits with closed fractures, hospitals should be considering moving to 0.7% iodine povacrylex in 74% isopropyl alcohol as the primary skin antiseptic for all fracture surgery.

Research Implications

The results of this thesis suggest that whether looking at alcohol-based or aqueous solutions, or at the primary ingredient of these solutions, little difference in the risk to surgical site infection is seen in an open fracture population. This may be due to the fact that the protective barrier that is the skin is broken well before the time of the incision in the operating room, and the deeper tissues already exposed to the skin flora well before any antiseptic solution is applied to the skin in a perioperative setting. This provides support to the idea that earlier is better with regards to interventions aimed at preventing infection in open fractures. This includes early systemic antibiotic prophylaxis, but also

new areas for research including the use of topical antibiotics as early as in the emergency department.[63,64]

Conclusion

This thesis work found that there was no evidence of any difference in the risk of SSI or unplanned reoperation when comparing alcohol-based and aqueous skin preparation solutions. Furthermore, while this analysis demonstrated no harm to using an alcohol-based solution for open fractures, the PREPARE trial found that for closed fractures skin preparation with 0.7% iodine povacrylex in 74% isopropyl alcohol had a reduced risk of SSI. Given these findings, surgeons should consider treating all fracture patients with 0.7% iodine povacrylex in 74% isopropyl alcohol to streamline policy with a single skin antiseptic for all fractures. This thesis also provides evidence of the benefits of master protocol approaches to multiple trials with differing hypotheses, as the standardization of patient eligibility and outcome assessment lends itself to further analysis as pooled patients populations in combined analyses.

References

1. Hofman K, Primack A, Keusch G, Hrynkow S. Addressing the growing burden of trauma and injury in low- and middle-income countries. *Am J Public Health*. 2005;95(1):13-17. doi:10.2105/AJPH.2004.039354
2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006;3(11):2011-2030. doi:10.1371/journal.pmed.0030442
3. Schade AT, Khatri C, Nwankwo H, Carlos W, Harrison WJ, Metcalfe AJ. The economic burden of open tibia fractures: A systematic review. *Injury*. 2021;52(6):1251-1259. doi:10.1016/j.injury.2021.02.022
4. Hadfield JN, Omogbehin TS, Brookes C, et al. TRAUMA The Open-Fracture Patient Evaluation Nationwide (OPEN) study EPIDEMIOLOGY OF OPEN FRACTURE CARE IN THE UK. *Bone Jt Open*. 2022;3(10):746-752. doi:10.1302/2633-1462.310.BJO-2022-0079.R1
5. Bhandari M, Jeray K, Petrisor B, et al. A Trial of Wound Irrigation in the Initial Management of Open Fracture Wounds. *New England Journal of Medicine*. 2015;373(27):2629-2641. doi:10.1056/nejmoa1508502
6. O'Hara NN, Mugarura R, Potter J, et al. The Socioeconomic Implications of Isolated Tibial and Femoral Fractures from Road Traffic Injuries in Uganda. *J Bone Joint Surg*. 2018;100(7):e43. doi:10.2106/JBJS.17.00439
7. O'Hara NN, Slobogean GP, Klazinga NS, Kringos DS. Analysis of Patient Income in the 5 Years Following a Fracture Treated Surgically. *JAMA Netw Open*. 2021;4(2). doi:10.1001/JAMANETWORKOPEN.2020.34898
8. O'Hara NN, Mugarura R, Potter J, et al. Economic loss due to traumatic injury in Uganda: The patient's perspective. *Injury*. 2016;47(5):1098-1103. doi:10.1016/J.INJURY.2015.11.047
9. Mundy LR, Zingas NH, McKibben N, et al. Financial Toxicity Is Common in Patients After Tibia Fracture. *J Orthop Trauma*. 2023;37(4):E147-E152. doi:10.1097/BOT.0000000000002520

10. Slobogean GP, Sprague S, Wells JL, et al. Aqueous skin antisepsis before surgical fixation of open fractures (Aqueous-PREP): a multiple-period, cluster-randomised, crossover trial. *The Lancet*. 2022;400(10360):1334-1344. doi:10.1016/S0140-6736(22)01652-X
11. Berner JE, Chan JKK, Gardiner MD, et al. International Lower Limb Collaborative (INTELLECT) study: a multicentre, international retrospective audit of lower extremity open fractures. *Br J Surg*. 2022;109(9):792-795. doi:10.1093/BJS/ZNAC105
12. Gustilo RB, Mendoza RM, Williams DN. Problems in the management of type III (Severe) open fractures: A new classification of type III open fractures. *Journal of Trauma*. 1984;24(8):742-746. doi:10.1097/00005373-198408000-00009
13. Lack WD, Karunakar MA, Angerame MR, et al. Type III open tibia fractures: Immediate antibiotic prophylaxis minimizes infection. *J Orthop Trauma*. 2015;29(1):1-6. doi:10.1097/BOT.0000000000000262
14. Major Extremity Trauma Research Consortium (METRC). Modern External Ring Fixation Versus Internal Fixation for Treatment of Severe Open Tibial Fractures: A Randomized Clinical Trial (FIXIT Study). *J Bone Joint Surg Am*. 2022;104(12):1061-1067. doi:10.2106/JBJS.21.01126
15. Whitehouse JD, Friedman ND, Kirkland KB, Richardson WJ, Sexton DJ. The Impact of Surgical-Site Infections Following Orthopedic Surgery at a Community Hospital and a University Hospital Adverse Quality of Life, Excess Length of Stay, and Extra Cost. *Infect Control Hosp Epidemiol*. 2002;23(4):183-189. doi:10.1086/502033
16. Meara JG, Leather AJM, Hagander L, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. *Lancet*. 2015;386(9993):569-624. doi:10.1016/S0140-6736(15)60160-X
17. O'Neill KM, Greenberg SLM, Cherian M, et al. Bellwether Procedures for Monitoring and Planning Essential Surgical Care in Low- and Middle-Income

Countries: Caesarean Delivery, Laparotomy, and Treatment of Open Fractures. *World J Surg*. 2016;40(11):2611-2619. doi:10.1007/S00268-016-3614-Y

18. Minehara H, Maruo A, Amadei R, et al. Open fractures: Current treatment perspective. *OTA Int*. 2023;6(3 Suppl):e240. doi:10.1097/oi9.0000000000000240
19. Gustilo RB, Merkow RL, Templeman D. The management of open fractures. *Journal of Bone and Joint Surgery - Series A*. 1990;72(2):299-304. doi:10.2106/00004623-199072020-00023
20. Mundi R, Chaudhry H, Niroopan G, Petrisor B, Bhandari M. Open tibial fractures: Updated guidelines for management. *JBJS Rev*. 2015;3(2):1-7. doi:10.2106/JBJS.RVW.N.00051
21. Castillo IA, Heiner JA, Meremikwu RI, Kellam J, Warner SJ. Where are we in 2022? A Summary of 11,000 Open Tibia Fractures over Four Decades. *J Orthop Trauma*. 2023;37(8):e326-e334. doi:10.1097/bot.0000000000002602
22. Ma N, Gogos S, Moaveni A. Do Intrawound Antibiotics Reduce the Incidence of Surgical Site Infections in Pelvic and Lower-Limb Trauma Surgery? A Systematic Review and Meta-analysis. *J Orthop Trauma*. 2022;36(11):E418-E424. doi:10.1097/BOT.0000000000002422
23. Qadir R, Costales T, Coale M, et al. Vancomycin Powder Use in Fractures at High Risk of Surgical Site Infection. *J Orthop Trauma*. 2021;35(1):23-28. doi:10.1097/BOT.0000000000001863
24. O'Toole R V., Joshi M, Carlini AR, et al. Effect of Intrawound Vancomycin Powder in Operatively Treated High-risk Tibia Fractures: A Randomized Clinical Trial. *JAMA Surg*. 2021;156(5):1-12. doi:10.1001/jamasurg.2020.7259
25. Awad ME, Chung JY, Griffin N, Stoneback JW, Alfonso NA. Prophylactic Intrawound Antibiotics Significantly Reduce the Risk of Deep Infections in Fracture Fixation: Subgroup Meta-analyses of the Type of Fracture, Antibiotics, and Organism. *J Orthop Trauma*. 2023;37(10):E400-E409. doi:10.1097/BOT.0000000000002641

26. Swenson BR, Hedrick TL, Metzger R, Bonatti H, Pruett TL, Sawyer RG. Effects of preoperative skin preparation on postoperative wound infection rates: a prospective study of 3 skin preparation protocols. *Infect Control Hosp Epidemiol*. 2009;30(10):964-971. doi:10.1086/605926
27. Tuuli MG, Liu J, Stout MJ, et al. A Randomized Trial Comparing Skin Antiseptic Agents at Cesarean Delivery. *N Engl J Med*. 2016;374(7):647-655. doi:10.1056/NEJMOA1511048
28. Darouiche RO, Wall MJ, Itani KMF, et al. Chlorhexidine-Alcohol versus Povidone-Iodine for Surgical-Site Antisepsis. *N Engl J Med*. 2010;362(1):18-26. doi:10.1056/NEJMOA0810988
29. McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. *Clin Microbiol Rev*. 1999;12(1):147-179. doi:10.1128/CMR.12.1.147
30. Williamson DA, Carter GP, Howden BP. Current and Emerging Topical Antibacterials and Antiseptics: Agents, Action, and Resistance Patterns. *Clin Microbiol Rev*. 2017;30(3):827-860. doi:10.1128/CMR.00112-16
31. Hagi A, Iwata K, Nii T, Nakata H, Tsubotani Y, Inoue Y. Bactericidal Effects and Mechanism of Action of Olanexidine Gluconate, a New Antiseptic. *Antimicrob Agents Chemother*. 2015;59(8):4551. doi:10.1128/AAC.05048-14
32. Nakata H, Tsubotani Y, Nii T, Hagi A, Inoue Y, Imamura T. Effects of olanexidine gluconate on preoperative skin preparation: an experimental study in cynomolgus monkeys. *J Med Microbiol*. 2017;66(5):678. doi:10.1099/JMM.0.000462
33. Petrisor B, Jeray K, Schemitsch E, et al. Fluid lavage in patients with open fracture wounds (FLOW): an international survey of 984 surgeons. *BMC Musculoskelet Disord*. 2008;9:7. doi:10.1186/1471-2474-9-7
34. Hampton J, Park SSW, Palazzi K, et al. The effect of preoperative skin preparation on clinical outcomes with incisional surgery: a network meta-analysis. *ANZ J Surg*. 2022;92(11):2859-2867. doi:10.1111/ans.17831
35. Jain A, Deshpande P, Yoon EW, Lee KS, McGeer A, Shah V. 2% aqueous vs alcohol-based chlorhexidine for skin antisepsis in VLBW neonates undergoing

peripheral venipuncture: a non-inferiority trial. *J Perinatol*. 2022;42(5):636-641. doi:10.1038/S41372-022-01337-1

36. Charles D, Heal CF, Delpachitra M, et al. Alcoholic versus aqueous chlorhexidine for skin antisepsis: the AVALANCHE trial. *CMAJ : Canadian Medical Association Journal*. 2017;189(31):E1008-E1016. doi:10.1503/CMAJ.161460
37. Slobogean GP, Sprague S, Wells J, et al. Effectiveness of Iodophor vs Chlorhexidine Solutions for Surgical Site Infections and Unplanned Reoperations for Patients Who Underwent Fracture Repair: The PREP-IT Master Protocol. *JAMA Netw Open*. 2020;3(4):e202215. doi:10.1001/jamanetworkopen.2020.2215
38. Hampton J, Park SSW, Palazzi K, et al. The effect of preoperative skin preparation on clinical outcomes with incisional surgery: a network meta-analysis. *ANZ J Surg*. 2022;92(11):2859-2867. doi:10.1111/ans.17831
39. Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. *Journal of Bone and Joint Surgery - American Volume*. 1976;58(4):453-458. doi:10.1007/978-1-4471-5451-8_138
40. Mead GE, Graham C, Billot L, et al. Update to the FOCUS, AFFINITY and EFFECTS trials studying the effect(s) of fluoxetine in patients with a recent stroke: statistical analysis plan for the trials and for the individual patient data meta-analysis. *Trials*. 2020;21(1):971. doi:10.1186/s13063-020-04875-1
41. Centers for Disease Control and Prevention (CDC). Surgical Site Infection (SSI). Published online 2017.
42. FAITH Investigators. Fracture fixation in the operative management of hip fractures (FAITH): an international, multicentre, randomised controlled trial. *The Lancet*. 2017;389(10078):1519-1527. doi:10.1016/S0140-6736(17)30066-1
43. Wise BT, Connelly D, Rocca M, et al. A Predictive Score for Determining Risk of Surgical Site Infection after Orthopaedic Trauma Surgery. *J Orthop Trauma*. 2019;33(10):506-513. doi:10.1097/BOT.0000000000001513

44. Schandelmaier S, Briel M, Varadhan R, et al. Development of the instrument to assess the credibility of effect modification analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ*. 2020;192(32):E901-E906. doi:10.1503/cmaj.200077
45. Sun X, Briel M, Busse JW, et al. Subgroup Analysis of Trials Is Rarely Easy (SATIRE): A study protocol for a systematic review to characterize the analysis, reporting, and claim of subgroup effects in randomized trials. *Trials*. 2009;10:101. doi:10.1186/1745-6215-10-101
46. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in Medicine — Reporting of Subgroup Analyses in Clinical Trials. *New England Journal of Medicine*. 2007;357(21):2189-2194. doi:10.1056/nejmsr077003
47. Sun X, Ioannidis JPA, Agoritsas T, Alba AC, Guyatt G. How to use a subgroup analysis users' guides to the medical literature. *JAMA*. 2014;311(4):405-411. doi:10.1001/jama.2013.285063
48. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ*. 2010;340(7751):850-854. doi:10.1136/bmj.c117
49. Chang Y, Bhandari M, Zhu KL, et al. Antibiotic Prophylaxis in the Management of Open Fractures. *JBJS Rev*. 2019;7(2). doi:10.2106/JBJS.RVW.17.00197
50. Allegranzi B, Bischoff P, de Jonge S, et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis*. 2016;16(12):e276-e287. doi:10.1016/S1473-3099(16)30398-X
51. Calderwood MS, Anderson DJ, Bratzler DW, et al. Strategies to prevent surgical site infections in acute-care hospitals: 2022 Update. *Infect Control Hosp Epidemiol*. 2023;44(5):695-720. doi:10.1017/ICE.2023.67
52. Stanton C. Guideline for preoperative patient skin antisepsis. *AORN J*. 2021;113(4):P5-P7. doi:10.1002/AORN.13380

53. Goldman AH, Tetsworth K. AAOS Clinical Practice Guideline Summary: Prevention of Surgical Site Infection After Major Extremity Trauma. *J Am Acad Orthop Surg*. 2023;31(1):E1-E8. doi:10.5435/JAAOS-D-22-00792
54. Sprague S, Slobogean G, Wells JL, et al. Skin Antisepsis before Surgical Fixation of Extremity Fractures. *New England Journal of Medicine*. 2024;390(5):409-420. doi:10.1056/nejmoa2307679
55. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/BMJ.39489.470347.AD
56. Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *The BMJ*. Published online 2019. doi:10.1136/bmj.l4898
57. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Online)*. 2011;343(7829). doi:10.1136/bmj.d5928
58. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol*. 2011;64(12):1283-1293. doi:10.1016/J.JCLINEPI.2011.01.012
59. Dumville JC, Mcfarlane E, Edwards P, Lipp A, Holmes A, Liu Z. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. *Cochrane Database Syst Rev*. 2015;2015(4). doi:10.1002/14651858.CD003949.PUB4
60. Leaper DJ. Risk factors for surgical infection. *J Hosp Infect*. 1995;30 Suppl:127-139. doi:10.1016/0195-6701(95)90013-6
61. Slobogean GP, Sprague S, Wells J, et al. Effectiveness of Iodophor vs Chlorhexidine Solutions for Surgical Site Infections and Unplanned Reoperations for Patients Who Underwent Fracture Repair: The PREP-IT Master Protocol. *JAMA Netw Open*. 2020;3(4):e202215. doi:10.1001/jamanetworkopen.2020.2215

62. Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *N Engl J Med*. 2017;377(1):62-70. doi:10.1056/NEJMRA1510062

63. Taylor S, John MP, Grayson W, Mir HR. The Effect of Topical Antibiotic Powder Application in the Emergency Department on Deep Fracture-Related Infection in Type III Open Lower Extremity Fractures. *J Orthop Trauma*. 2024;38(1):3-9. doi:10.1097/BOT.0000000000002717

64. Burbank KM, Schauer SG, De Lorenzo RA, Wenke JC. Early application of topical antibiotic powder in open-fracture wounds: A strategy to prevent biofilm formation and infections. *OTA International*. 2020;3(4):e091-e091. doi:10.1097/OI9.0000000000000091