

ORIGINAL ARTICLE

# A Trial of Wound Irrigation in the Initial Management of Open Fracture Wounds

The FLOW Investigators

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The initial management of open fractures requires thorough irrigation and débridement[1-4] to prevent infection and promote wound and bone healing.[2,4] Clinicians accomplish débridement by removing all visible debris and necrotic tissue and by providing copious irrigation of the wound.

Controversy exists regarding the choice of irrigation pressure and solution.[4-13] High pressure may be more effective than low pressure in removing particulate matter and bacteria[7-10] but at the expense of bone damage[8,11] and a resultant delay in bone healing.[12] Low pressure may avoid bone damage and delayed healing but at the possible cost of less effective removal of foreign matter and bacteria.

Regarding the preferred irrigation solution, there is a strong biologic rationale for the use of surfactants, such as soap.[14-20] Because soap contains both nonpolar and polar molecules, it acts as an emulsifier, dispersing one liquid, or particulate, into another immiscible liquid. As compared with other enhanced irrigation solutions (i.e., those that contain antiseptic or antibiotic agents), soap is less expensive,[21] does not have a risk of antibiotic resistance,[14] and is less toxic.[1,7,17-19,22,23]

To address these issues regarding irrigation pressures and solutions, we conducted the Fluid Lavage of Open Wounds (FLOW) trial in patients requiring surgery for open fracture. We examined the effect of alternative pressures and castile soap versus normal saline irrigation on a composite of a number of different reasons for reoperations within 12 months after the index surgery.

## METHODS

### Study Design

Our study was an international, blinded, randomized, controlled trial that used a 2-by-3 factorial design to evaluate the effects of high versus low versus very low (gravity flow) irrigation pressures and soap versus normal saline solutions on reoperation rates among patients with an open fracture. The objectives and methods of the trial were published previously.[24] The study was approved by the ethics committees at McMaster University, Greenville Health System, and each participating center. All the patients provided written informed consent.

### Study Oversight

The study was funded by the Canadian Institutes of Health Research, the U.S. Department of Defense, and others. The Clinical Advances through Research and Information Translation (CLARITY) Research Group at McMaster University coordinated the trial and was responsible for the trial randomization, the maintenance, validation, and analysis of the data, and the study-center coordination. The Greenville Health System assisted in the coordination of study sites in the United States. Stryker donated Surgilav irrigators for the trial for clinical sites in Asia. Zimmer provided the Pulsavac irrigator at a reduced cost to selected clinical sites in North America. Triad Medical donated castile soap; castile soap from Aplicare was purchased at full cost. No donor or funder had a role in the design or conduct of the study, the collection or analyses of the data, or the preparation of the manuscript.

The steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org), chaired by the principal investigators, designed the trial and prespecified the statistical analysis plan. The members of the steering committee vouch for the completeness and accuracy of the data and analyses reported and for the adherence of the trial to the protocol,

available at NEJM.org. The first author, who was the chair of the writing committee, wrote the first draft of the manuscript; all the members of the writing committee made revisions and made the decision to submit the manuscript for publication.

### Patients

From June 2009 through September 2013, we recruited patients across 41 sites in the United States, Canada, Australia, Norway, and India. Eligible patients were 18 years of age or older with an open fracture of an extremity that required operative fixation. Extremity was defined as arm, wrist, leg, ankle, foot, clavicle, or scapula. We excluded fractures of the pelvic ring and axial skeleton and fractures of the hand (metacarpals and phalanges) and toes (phalanges). Detailed eligibility criteria are listed in the Supplementary Appendix.

### Procedures

Patients were stratified according to study center and Gustilo–Anderson fracture grade (I or II vs. III) (see the Supplementary Appendix). Patients underwent randomization in a 1:1:1:1:1:1 ratio and were assigned to one of six treatment groups: soap and very low pressure, soap and low pressure, soap and high pressure, saline and very low pressure, saline and low pressure, or saline and high pressure. Randomization was performed with the use of a central computerized system with variable block sizes, thus ensuring concealment of the study-group assignments. Patients, end-point adjudicators, and data analysts were unaware of the study-group assignments.

During surgery, the initial management of the open fracture included irrigation that was delivered by means of very low pressure (1 to 2 psi), low pressure (5 to 10 psi), or high pressure (>20 psi). In the operating room, surgeons used a sterile technique to prepare either a 0.45% solution of castile soap (Triad Medical and Aplicare) in normal saline (see the Supplementary Appendix) or used sterile normal saline alone. We standardized the perioperative antibiotic regimens and the minimum amount of solution according to the severity of the open fracture wound, which was graded according to the Gustilo–Anderson classification (3 liters for grade I fracture and 6 liters for grade II or III) (see the Supplementary Appendix).[2]

Patients returned for follow-up assessments at 1, 2, and 6 weeks and 3, 6, 9, and 12 months after surgery. Details of the follow-up process are provided in the Supplementary Appendix.

### Study End Points

The primary end point was reoperation, defined as surgery that occurred within 12 months after the initial procedure to treat an infection at the operative site or contiguous to it, manage a wound-healing problem, or promote bone healing. The procedures included in this composite end point were the following: irrigation and débridement for an infected wound; revision and closure for wound dehiscence; wound coverage for an infected or necrotic wound; drainage of a hematoma; reoperation for hardware failure that was probably related to an infection, wound-healing problem, or bone-healing problem (e.g., delayed union or nonunion); bone grafting or implant-exchange procedure for established nonunion in patients with a postoperative fracture gap of less than 1 cm; intramedullary nail dynamizations in the operating room (dynamization involves removal of locking screws from the intramedullary nail to allow fracture ends to compress with weight bearing); fasciotomies for the compartment syndrome; and other events as determined by the adjudication committee. Full details are provided in the Supplementary Appendix. Secondary end points included nonoperatively managed infection and wound-healing and bone-healing problems within 12 months after the index surgery.

A central adjudication committee, whose members were unaware of the study-group assignments, adjudicated all primary and key secondary end points. To minimize random error, the committee blindly adjudicated trial eligibility on the basis of data available before or shortly after randomization (see the Supplementary Appendix).[25]

### Statistical Analysis

We originally calculated that the sample size would have to be 2280 patients, with 1140 patients per solution group and 760 patients per pressure group. This sample size was based on the size of the irrigation-pressure groups and was calculated to ensure that the study would have a power of 80% to identify differences among the three irrigation-pressure groups in effects of pairwise comparisons at an adjusted alpha level of 0.0188, on the basis of a rate of reoperation within 12 months of 30% in a control group and a 25% lower relative risk with one irrigation pressure than with another. We estimated a similar control-group reoperation rate for normal saline,[13,26,27] and the study therefore also had 98% power to detect a 25% lower relative risk with soap — a treatment effect that was endorsed by 80% of surgeons in our international survey as important enough to change practice.[13]

An interim analysis was performed in January 2013 after 2079 patients had been enrolled; 789 of these patients had 12-month outcomes available. The external data and safety monitoring committee considered the O'Brien–Fleming stopping criterion that specifies a significance level that maintains the overall type I error rate of 0.05,[28] and the committee recommended the recruitment of additional patients in the trial to account for a projected 10% loss to follow-up. We recruited a total of 2551 patients.

The analyses included all the patients in the groups to which they were randomly assigned. For patients for whom 12-month follow-up information was unavailable, data were included to the date of their last documented follow-up and were censored at that time. The CLARITY Research Group data analyst remained unaware of the treatment-group assignments while conducting the primary analyses.

Using Cox regression stratified according to fracture grade (I or II vs. III) and study center, we first conducted a time-to-event analysis of the main effects with respect to solution and pressure and the interaction between the two with regard to the reoperation rate. If the interaction was significant, we planned to explore the nature of the effect modification.

Our primary analysis was a Cox regression stratified according to the severity of the open fracture[2] and study center, with reoperation as the end point in the time-to-event analysis. The Cox regression to investigate the effect of irrigation pressure was also stratified according to irrigation solution. Similarly, the irrigation-solution analysis was stratified according to irrigation pressure. We also performed analyses, using Cox regression, that were adjusted for age, injury (upper extremity vs. lower extremity), fracture gap (<1 cm vs. ≥1 cm), type of internal fixation (intramedullary nail, external fixator, plate, other internal fixation, other fixation, or none), and severity of wound contamination (mild vs. moderate vs. severe). For both the primary and adjusted analyses, we tested the proportional-hazards assumption.

We examined the three-category randomized pressure variable for statistical significance at an alpha level of 0.05; if the results were significant, we planned to conduct pairwise comparisons using an alpha level of 0.0188. In instances of significant differences between results, we conducted a sensitivity analysis that was based on plausible differences in event rates among patients lost to follow-up versus those for whom follow-up was complete.[29] In this case, we tested the effect of assuming that in the saline group, the event rate among patients who were lost to follow-up would be twice as high as the rate among those successfully followed. All the analyses were performed with the use of SAS software, version 9.2 (SAS Institute).

Before unblinding and as described in our statistical analysis plan, we prespecified 12 subgroup analyses that explored a possible modification of the effect of alternative irrigation pressures and solutions in subgroups defined according to fracture severity, location of fracture (upper vs. lower extremity, tibial vs. nontibial fracture, and intraarticular vs. extraarticular involvement), and aspects of the surgical wound débridement. We conducted an additional post hoc subgroup analysis that evaluated the possible effect modification according to time to surgery (<6 hours, 6 to 12 hours, or >12 hours after injury). We used multiple criteria to consider the credibility of any possible subgroup effects.[30] The Supplementary Appendix provides details regarding hypothesized subgroup effects.

We first interpreted the results on the basis of a blinded review of the results of our primary analysis.[31] The randomization code was then broken, the correct interpretation chosen, and the draft of the manuscript was written. The Supplementary Appendix provides details regarding specific analyses and our blinded interpretation.

## RESULTS

### Patients

From June 2009 through September 2013, we randomly assigned 859 of 2551 enrolled patients to the high-pressure group, 846 to the low-pressure group, and 846 to the very-low-pressure group. A total of 1275 patients were assigned to irrigation with soap and 1276 to irrigation with normal saline. Of 2551 patients enrolled, the adjudication committee (whose members were unaware of the treatment assignments) determined that 104 patients were ineligible owing to no receipt of surgical treatment (47 patients), incorrect fracture type (48), history of osteomyelitis (1), retained hardware from a previous fracture in the same extremity (2), use of immunosuppressive medication (2), or age (4). The remaining 2447 patients were included in the final analyses, with the patients' data analyzed in the treatment groups to which the patients had been randomly assigned. We obtained 12-month follow-up data for 90% of the patients (Figs. S1 and S2 in the Supplementary Appendix).

The majority of patients were men, were in their 40s, were those with a lower-extremity fracture, and were those with no concomitant major trauma. The most common mechanism of injury was motor vehicle accident. The characteristics were similar in the randomized study groups (Table 1). Typical patients underwent plate fixation, underwent their first irrigation within 10 hours after their injury, and received antibiotic prophylaxis; the treatments, including volumes of irrigation solutions, were similar in the randomized study groups (Table 1, and Tables S1 and S2 in the Supplementary Appendix).

**TABLE 1**



Characteristics of the Patients and Surgical and Perioperative Treatment.

### Adherence to Assigned Intervention

Adherence by the surgeon to the initially assigned irrigation pressure ranged from 96.5% to 98.8%. Adherence by the surgeon to the initially assigned irrigation solution was 97.9% in the soap group and 99.6% in the saline group (Tables S3 and S4 in the Supplementary Appendix).

### Interaction between Irrigation Pressures and Solutions

Results showed no interaction between solution and pressure (P=0.31). Therefore, we completed separate analyses for irrigation pressures and solutions.

### Primary End Point

*According to Irrigation Pressure*

A primary study end-point event, reoperation within 12 months after the index procedure in order to treat an infection, manage a wound-healing problem, or promote bone healing, occurred in 323 of the 2447 patients (13.2%). The rate of the primary end point did not differ significantly according to type of irrigation pressure: 109 of 826 patients (13.2%) in the high-pressure group had a primary end-point event, as did 103 of 809 patients (12.7%) in the low-pressure group and 111 of 812 (13.7%) in the very-low-pressure group (P=0.80 for the three-way comparison). Hazard ratios were as follows: for low pressure versus high pressure, 0.92 (95% confidence interval [CI], 0.70 to 1.20; P=0.53); for high pressure versus very low pressure, 1.02 (95% CI, 0.78 to 1.33; P=0.89); and for low pressure versus very low pressure, 0.93 (95% CI, 0.71 to 1.23; P=0.62) (Table 2 and Figure 1A). Adjusted analyses yielded similar results (Table S5 in the Supplementary Appendix).

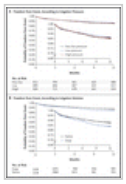
**TABLE 2**

Study End Points for the Comparison of Irrigation Pressures.

*According to Irrigation Solution*

The rate of the primary end point differed significantly according to type of irrigation solution: 182 of 1229 patients (14.8%) in the soap group had a primary end-point event, as compared with 141 of 1218 (11.6%) in the saline group (hazard ratio in the soap group, 1.32; 95% CI, 1.06 to 1.66; P=0.01) (Table 3 and Figure 1B). Adjusted analyses yielded similar results for the effect of solution (Table S6 in the Supplementary Appendix).

**FIGURE 1**



Kaplan–Meier Estimates of Freedom from the Primary End Point.

The frequency of all components of the primary end point was higher in the soap group than in the saline group. The frequency of implant-exchange procedures for established nonunion in patients with a fracture gap of less than 1 cm was significantly higher in the soap group than in the saline group (hazard ratio, 1.59; 95% CI, 1.01 to 2.51; P=0.046) (Table 3). Our sensitivity analysis showed that if we assumed that the patients who were lost to follow-up in the soap group had the same risk of the primary end point as those who had complete follow-up and that the patients who were lost to follow-up in the saline group had a risk of the primary end point that was twice as high as the risk among those with complete follow-up, then the study would lose statistical significance of the effect of soap versus saline (P=0.16).

### Secondary End Points

We found no significant differences among the three irrigation pressures with respect to the secondary end points of nonoperatively managed infection, wound-healing problem, and bone-healing problem (Table 2). Likewise, we found no significant differences between the two irrigation solutions with respect to any of the secondary end points (Table 3).

**TABLE 3**

Study End Points for the Comparison of Irrigation Solutions.

### Subgroup Analyses

Subgroup analyses of the various irrigation pressures and solutions yielded results that were consistent with the primary treatment effects for each intervention. The exceptions were tibial versus nontibial fracture, for which the results suggested a trend toward superiority of very low pressure over low or high pressure in patients with a tibial fracture, and a similarity in the soap group and the saline group when the duration of antibiotic use after surgery was 4 days or more (Figure 2, and Tables S7 and S8 in the Supplementary Appendix).

**FIGURE 2**

Subgroup Analyses of the Primary End Point, According to Irrigation Solution.

## DISCUSSION

We found no significant influence of irrigation pressure on our composite primary end point of various forms of reoperation for treatment of infection, wound-healing problem, or bone-healing problem within 12 months after the initial surgery. The irrigation of open fracture wounds with soap, as compared with saline solution, was associated with a significantly higher rate of reoperation within 12 months. The effects of the irrigation pressures and solutions were consistent across all components of the primary end point. No significant differences in the rates of secondary end points (nonoperatively managed infection, wound-healing problem, and bone-healing problem) were observed between the two irrigation solutions or among the three irrigation pressures.

A possible effect modification was observed in two subgroups: subgroup analyses suggested that very low pressure was superior to low or high pressure in patients with a tibial fracture but inferior in patients with other fractures (P=0.05 for interaction) and that saline solution was superior to soap

when antibiotics were given for less than 4 days after surgery, but saline and soap were similar when antibiotics were given for 4 or more days (P=0.03 for interaction). Because many subgroup analyses were performed, the positive results in these two subgroups have relatively low credibility.[30]

Our study had several strengths. We included safeguards against potential bias (concealed randomization and concealment of study-group assignments from patients, end-point adjudicators, and data analysts) and safeguards against interpretation bias.[31] The study also had broad inclusion criteria with a large number of centers in countries with diverse health care systems, as well as a focus on an end point (i.e., reoperation) that is of unequivocal importance to both patients and the health care system.

Our study has certain limitations. Although the surgeons had high adherence to the initial irrigation protocol during the index surgery, the rate of surgeons' adherence to the originally assigned pressure and solution for the 615 patients who required a secondary operative irrigation and débridement decreased to 75.9% for irrigation pressure and 79.3% for irrigation solution. This level of adherence is still relatively high, and we found a detrimental effect of soap that any intervention crossover would tend to obscure.

Our estimates of the treatment effect of high versus low pressure, high versus very low pressure, and low versus very low pressure, although close to 1.0, exclude large differences but do not exclude small but potentially important differences. For instance, on the basis of the 95% confidence intervals, our results are consistent with high-pressure irrigation resulting in either 22% fewer operations or 33% more operations as compared with very low pressure.

A total of 10% of the patients who underwent randomization were not followed to 12 months; the survival analysis included available data for these patients. The finding of the superiority of saline to soap was not robust to a sensitivity analysis that assumed that patients in the saline group who were lost to follow-up had a risk of event that was twice as high as the risk among those with complete follow-up. This analysis reduces our strength of inference that soap is inferior, but it does not undermine the conclusion that soap is no better than saline. The use of a single concentration of soap solution limited our ability to explore a potentially efficacious dose. It is plausible that the soap-solution concentration (0.45%) was too high and that a lower concentration might have been effective. Our choice of castile soap and dosing was, however, based on a large body of experimental evidence,[7,14-19] a recent clinical trial that used this formulation[21] without adverse effects, and our pilot study, which suggested its safety.[27]

Our trial defined the highest pressure category as 20 psi or higher, whereas prior experimental studies have used pressures of more than 50 psi. Our cutoff points for pressure were based on a prior survey of surgeons and on the American College of Surgeons definition of high pressure as 15 to 35 psi and low pressure as 1 to 15 psi. We further subcategorized the low-pressure category to low (5 to 10 psi) and very low (1 to 2 psi), given the available settings on the handheld, battery-operated irrigators in this trial.

A prior randomized trial addressed the relative effect of irrigation pressures on patient-important outcomes.[32] That trial, which involved 335 patients who presented to the emergency department with open wounds within 24 hours after injury, compared pressures of 13 psi (intermediate between our low and high pressures) with very low pressure (1 to 2 psi) administered with a bulb syringe. The authors found a significantly lower rate of wound infection with the higher pressure (1.3% vs. 6.9%, P=0.02). That study did not conceal randomization assignments, did not blind the assessment of infections, and had a high loss to follow-up (19% of patients). The methodologic differences between that study and ours may explain the differences in outcomes.

Our results challenge the results of prior studies, guidelines, and a large body of experimental evidence that have favored higher pressures (typically >20 psi) for the effective removal of contaminants. A number of nursing guidelines recommend high-pressure irrigation.[33-35] Although surgical and orthopedic organizations do not provide guidance on irrigation pressures, several expert authors suggest the use of irrigation pressures between 8 and 12 psi.[5,6]

Experimental evidence has suggested that irrigation pressures of less than 10 psi are ineffective in removing soil contaminants from contaminated open wounds.[5] Experimental studies have also shown that high-pressure irrigation is more effective than low-pressure irrigation in the removal of bacteria, especially when the time to irrigation was delayed beyond 6 hours.[36] In contrast, some experimental studies have shown complications from high-pressure irrigation, including increased damage to fractured bone,[37] bacterial propagation into soft tissues and the intramedullary canal of the fractured bone,[11,37] promotion of stem-cell differentiation from bone-forming cells (osteoblasts) toward the adipocyte cell type,[38] and impairment of in vivo fracture healing.[12] Our results suggest that findings from experimental studies do not always translate into differences in patient-important outcomes in clinical practice.

With regard to irrigation solutions, our findings contrast with those of prior experimental studies[1-7,14-21,27] in laboratory and animal models that showed soap solution to be more effective than

normal saline in removing bacteria and particulate matter from wounds and bone,[7,14,16,17] without toxic effects to soft tissues and bone.[7] One trial involving 400 patients showed that, at a mean follow-up of 1.3 years, a 0.45% soap solution was associated with a lower risk of infection than the risk with an antibiotic solution (100,000 U of bacitracin per 3 liters of normal saline) (13% vs. 18%; relative risk, 0.74; 95% CI, 0.45 to 1.26),[21] and a lower risk of wound-healing complications (4% vs. 10%, P=0.03). That trial, however, had unblinded outcome adjudication and appeared to have unconcealed randomization; there was also bias in that soap was compared with normal saline that contained antibiotics. The point estimate from our randomized FLOW pilot trial, which involved 111 patients, also favored the soap solution over normal saline (hazard ratio, 0.77; 95% CI, 0.35 to 1.69).[27]

Some experimental data support the results of our clinical trial. In an established animal model of a contaminated complex musculoskeletal wound, the initial reduction in pseudomonas bacterial counts was greater when wound irrigation was performed with castile soap than when it was performed with normal saline (with counts reduced to 13% vs. 29% of the pretreatment level),[39] but at 48 hours, bacterial counts in the soap group increased to 120% of the pretreatment levels, whereas the bacterial counts with normal saline solution were 68% of the pretreatment levels. Similarly, investigators using a *Staphylococcus aureus*–contaminated rat-femur model have suggested that host-tissue toxicity and necrosis from antibacterial solutions allow bacteria to thrive and bacterial levels to rebound to pretreatment levels.[40]

Our study may have implications for the care of patients with open fractures worldwide and may inform protocols for the management of wound irrigation for paramedics, nurses, emergency physicians, and surgeons caring for patients with open fractures. Our findings may be particularly relevant for low-income and middle-income countries, in which 90% of the road traffic fatalities globally, and probably a similar percentage of open fractures, occur.[41] In such contexts, the knowledge that there is no benefit to the use of irrigation-pressure devices can guide the allocation of limited resources — a result that is also very important for the management of open fractures in combat settings.

In conclusion, our results suggest similar reoperation rates regardless of irrigation pressure and establish very low pressure as an acceptable, low-cost alternative in the irrigation of open fractures. Our findings indicate that saline was superior to castile soap solution for the routine irrigation of acute open fractures.

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The members of the writing committee (Mohit Bhandari, M.D., Ph.D., Kyle J. Jeray, M.D., Brad A. Petrisor, M.D., P.J. Devereaux, M.D., Ph.D., Diane Heels-Ansdell, M.Sc., Emil H. Schemitsch, M.D., Jeff Anglen, M.D., Gregory J. Della Rocca, M.D., Ph.D., Clifford Jones, M.D., Hans Kreder, M.D., M.P.H., Susan Liew, M.B., B.S., Paula McKay, B.Sc., Steven Papp, M.D., Parag Sancheti, M.B., B.S., M.Ch., D.N.B., Sheila Sprague, Ph.D., Trevor B. Stone, M.D., Xin Sun, Ph.D., Stephanie L. Tanner, M.S., Paul Tornetta III, M.D., Ted Tufescu, M.D., Stephen Walter, Ph.D., and Gordon H. Guyatt, M.D.) assume responsibility for the overall content and integrity of the article.

## SOURCE INFORMATION

The affiliations of the members of the writing group are as follows: Division of Orthopaedic Surgery, the Department of Surgery (M.B., B.A.P., S.S.), the Departments of Clinical Epidemiology and Biostatistics (M.B., P.J.D., D.H.-A., P.M., S.S., S.W., G.H.G.) and Medicine (P.J.D., G.H.G.), and the Population Health Research Institute (P.J.D.), McMaster University, Hamilton, ON, the Division of Orthopaedic Surgery (H.K., E.H.S.) and Health Policy Management and Evaluation (H.K.), University of Toronto, and Sunnybrook Health Sciences Centre (H.K.), Toronto, the Division of Orthopaedic Surgery, University of Ottawa, Ottawa, ON (S.P.), the Department of Orthopaedics, Faculty of Medicine,

University of British Columbia, Vancouver (T.B.S.), and the Department of Surgery, University of Manitoba, Winnipeg (T.T.) — all in Canada; the Department of Orthopedic Surgery, Greenville Health System, Greenville, SC (K.J.J., S.L.T.); the Department of Orthopedic Surgery, Indiana University, Indianapolis (J.A.); the Department of Orthopedic Surgery, University of Missouri School of Medicine, Columbia (G.J.D.R.); Center for Orthopedic Research and Education Institute, Phoenix, AZ (C.J.); the Department of Surgery, Monash University, Melbourne, VIC, Australia (S.L.); Sancheti Institute for Orthopedics and Rehabilitation, Pune, India (P.S.); Chinese Evidence-based Medicine Center, Sichuan University, Chengdu, China (X.S); and the Department of Orthopedic Surgery, Boston University School of Medicine, Boston (P.T.).

Address reprint requests to Dr. Bhandari at the Division of Orthopaedic Surgery, McMaster University, 293 Wellington St. N., Suite 110, Hamilton, ON L8L 8E7, Canada, or at bhandam@mcmaster.ca.

A complete list of the Fluid Lavage of Open Wounds (FLOW) Investigators is provided in the Supplementary Appendix, available at NEJM.org.