PROGNOSIS AND MANAGEMENT OF TRAUMA PATIENTS

PROGNOSIS AND MANAGEMENT OF PATIENTS WHO HAVE INJURIES NECESSITATING ORTHOPEDIC SURGERY

By

YAPING CHANG, M.Sc.

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AUTHOR: Yaping Chang, M.Sc.

SUPERVISOR: Distinguished Professor Gordon Guyatt

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ABSTRACT

The current thesis aims to address the prognosis and management of patients who have injuries necessitating orthopaedic surgery.

In Chapter 1 I introduce the thesis, and in Chapter 5 I offer conclusions and summarize the contribution of the work. In Chapter 5, I address the scope, rationale, key findings, limitations and implications.

Chapter 2 is a systematic review and meta-analysis investigating the effectiveness of antibiotic prophylaxis in patients with open fracture of the extremities. The results demonstrate moderate quality evidence of an important reduction in the infection rate in patients receiving, versus not receiving, antibiotic prophylaxis. We found no difference in infection rate with longer (3 to 5 days) versus shorter (1 day) duration of antibiotics – this finding warrants only low confidence.

Chapter 3 is a systematic survey of current practice and recommendations regarding antibiotic prophylaxis in open fracture management. Authors of publications over the last decade strongly support early systemic antibiotics prophylaxis for patients with open fractures of extremities. In practice, most used systemic antibiotics with both gram-positive and gram-negative coverage, and continued the administration for 2 to 3 days. Most recommendations suggested gram-positive coverage for less severe injuries, and administration duration of no more than 3 days (half suggested 1 day). For more severe injuries, most

recommendations suggested broad antimicrobial coverage continued for 2 to 3 days.

Chapter 4 is a longitudinal study investigating predictors of persistent post-surgical pain after tibia fracture. We found significant independent associations between resolution of pain and male sex, non-smoking and alcohol consumption. Age, obesity, type of fracture (closed versus open), additional injuries, and post-operative weight-bearing status did not predict resolution of pain. Our findings suggest that clinicians should be particularly alert to the possibility of troublesome post-operative pain in female smokers who do not drink alcohol. Clinicians may consider counselling patients to discontinue smoking, inform them that they are at nearly double the risk of incidence of troublesome post-operative pain (in addition to the long-term adverse health consequences of smoking).

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LIST OF ABBREVIATIONS

BMI – Body Mass Index

CENTRAL – Cochrane Central Register of Controlled Trials

CI – Confidence Interval

CIHI – Canadian Institute for Health Information

CIHR – Canadian Institutes of Health Research

CINAHL – Index to Nursing and Allied Health

EMBASE – Excerpta Medica Database

FLOW – Fluid lavage of open wounds

GRADE – Grading of Recommendations Assessment, Development, and Evaluation

HR – Hazard Ratio

MRSA – Methicillin-resistant *Staphylococcus aureus*

PMMA – Polymethyl Methacrylate

PPSP – Persistent Post-surgical Pain

RCT – Randomized Controlled Trial

RR – Risk Ratio; Relative Risk

SD – Standard Deviation

TRUST – Trial to Re-evaluate Ultrasound in the Treatment of Tibial Fractures

MEDLINE – Medical Literature Analysis and Retrieval System Online

VIF – Variance Inflation Factor

WHO – the World Health Organization

DECLARATION OF ACADEMIC ACHIEVEMENT

This is a "sandwich" thesis that consists of five chapters, one of which has been published in a peer-reviewed medical journal (Chapters 2), and two of which has been submitted to a peer-reviewed medical journal but not yet accepted (Chapter 3 and Chapter 4). I am the first author and principle contributor of each chapter in this thesis. My supervisors, Drs. Gordon Guyatt, Mohit Bhandari, Jason Busse and Lehana Thabane, and I myself played the primary role in the conception and design of the study. My independent contributions included drafting each chapter's study protocol; performing the literature search, designing data abstraction forms, screening titles, abstractions and full texts, collaborating calibration of co-authors for the systematic reviews; cleaning data of TRUST; conducting analyses; designing figures and tables; drafting and critically revising the manuscripts; providing final approval of the versions submitted; and taking responsibility for all aspects of each chapter. I completed all aspects of this thesis between October 2014 and December 2017.

CHAPTER 1

Introduction

The principal objective of this thesis was to address prognosis and management of patients who had orthopedic injuries, in particular long bone fractures, addressing the role of antibiotic prophylaxis and predictors of persistent post-surgical pain.

Musculoskeletal injuries are a major cause of disability worldwide, particularly in individuals under 60 years of age [1-4]. Estimates show that by 2020, disability from traffic accidents will rank in the top 3 of all causes of disability [5]. Extremity injuries are the most common type of musculoskeletal injuries and represent approximately 65% of all injury admissions to hospitals [6]. The Canadian Institute for Health Information reports 257,439 musculoskeletal injury-related hospitalizations in Canada in 2015-2016 [7]. Globally, trauma-related care costs are over 100 billion dollars per year [1,3].

Open fractures – fractures associated with soft tissue compromise that result in a communication of the fracture ends with the external environment – are considered to be contaminated wounds [2,4,8]. The rate of fracture site infections varies, from 3% in less severe fractures to up to 50% in more severe open fractures [2,9]. Infection is an important cause of wound healing problems, and the subsequent development of nonunion and continued osseous instability. The infection, and wound healing complications associated with infection have a significant impact on the patients' quality of life and cost of health care [2-5,9].

Given the certainty of contamination and the very high incidence of infection, prophylactic use of antibiotics after open fracture has become routine [2-5]. Some authorities recommend giving intravenous antibiotics, most frequently suggested regimens being first or second generation cephalosporins, as early as possible to the patients with open fractures as prophylaxis for infection [4,8,10]. However, debate regarding the duration of use, the choice of antibiotics and the dosage continue. In practice, the individual treating surgeon or emergency room doctor typically chooses the type of antibiotic, dose, route of delivery and duration depending on department protocols or their individual preferences [11].

Therefore we undertook systematic reviews of the available evidence to investigate the impact of antibiotic prophylaxis in patients with open fractures. When our team discussed the research protocol, we realized that we had to take two steps to address the topic "A Systematic Review of Antibiotic Prophylaxis in the Management of Open Fractures".

Step One was to answer question of the evidence regarding the effectiveness of antibiotic prophylaxis. We therefore conducted a systematic review and meta-analyses of randomized controlled trials (RCTs) to address there specific questions: A) the impact of antibiotic prophylaxis versus no prophylaxis on rate of infection; B) the impact of longer versus shorter duration of antibiotic prophylaxis on rate of infection; and C) the impact of alternative antibiotics on rate of infection. We searched CINAHL, EMBASE, MEDLINE, CENTRAL, and the Cochrane database of systematic reviews from 1965 to December 2013. The quantitative synthesis included two meta-analyses: 4 RCTs compared antibiotic

versus no antibiotic, and 3 RCTs compared longer versus shorter course. The narrative summary included 10 other RCTs with interventions too diverse to pool their results. I include this systematic review, which was published in the JBJS Reviews in 2015, as Chapter 2 of the current thesis. Prior to my submission of the current thesis, we updated the search in above mentioned literature databases on January 7, 2018. We did not find any newly published RCTs between December 2013 and January 2018 to be eligible to our research question.

We undertook Step Two to answer questions of what regimens surgeons are currently using and what regimens experts are currently recommending as prophylaxis. We undertook a systematic survey of reports of surgeons' practice in the use of prophylactic antibiotics, and a complementary systematic survey of the available expert recommendations. We fully considered suggestions and expert opinion of our team and decided to include all articles, textbooks, guidelines and institutional protocols that were published in recent 10 years. We summarized antibiotic regimens, dose, time to antibiotic administration and duration for practice and recommendations. I include this study, which was submitted to the JBJS Reviews in December 2017, as Chapter 3 of the current thesis.

The background and inclusion criteria for Chapters 2 and 3 are similar. The search strategies for the published articles in Chapter 3 are the same as those in Chapter 2. However, the two studies deal with fundamentally different questions, and thus fundamentally different sources of evidence. Chapter 2 includes only RCTs; Chapter 3 includes RCTs and observational studies, as well as textbooks, guidelines and protocols. In Chapter 2, we searched for all eligible studies from

the relevant databases from inception to the date of the search. In Chapter 3, we searched for all eligible publications in recent ten years from January 2007 to June 2017.

Chapter 4 aims to address the association between baseline characteristics and persistent post-surgical pain (PPSP) among patients with a tibial shaft fracture. PPSP is common amongst patients who undergo surgery following lower extremity fractures. A prior prospective cohort study reported that 33.3% had moderate or severe pain intensity among patients with tibia fractures at 7 years after injury [12]. Greater duration and severity of post-surgical pain is associated with less mobility, restrictions in activities of daily living, and reduced quality of life [13]. Predictors of PPSP after fracture repair have received limited study. We used data collected as part of the Trial to Re-evaluate Ultrasound in the Treatment of Tibial Fractures (TRUST) and used a multivariable Cox proportional hazards regression model for analysis.

In Chapter 5, I summarized the key findings, addressed limitations, and discussed directions of future studies.

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CHAPTER 2

Effects of Antibiotic Prophylaxis in Patients with Open Fracture of the Extremities: A Systematic Review of Randomized Controlled Trials

At the time of writing this thesis, this chapter has been published in a peer-reviewed scientific journal, as follows:

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Effects of antibiotic prophylaxis in patients with open fracture of the extremities: a systematic review of randomized controlled trials

Yaping Chang, MSc[1], Sean Alexander Kennedy[2], Mohit Bhandari, PhD, MD[3], Luciane Cruz Lopes, PhD[4], Cristiane de Cássia Bergamaschi, PhD[4], Maria Carolina de Oliveira e Silva, MSc[4], Neera Bhatnagar, MLIS[5], S. Mohsen Mousavi, MD[6], Saqib Khurshid, MBBS[2], Brad Petrisor, MD[3], Melody Ren, BSc[2], Sukhmani K Sodhi[7], Reza Donald Mirza, BSc[2], Gordon H Guyatt, MD[1]

Affiliations and Correspondence

1. Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada

2. Michael G DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada

3. Division of Orthopaedic Surgery, Department of Surgery, McMaster University, Hamilton, Ontario, Canada

4. Pharmaceutical Sciences Postgraduate Course, University of Sorocaba, UNISO, Sorocaba, Sao Paulo, Brazil

5. Health Science Library, McMaster University, Hamilton, Ontario, Canada

6. asim, Swiss Academy of Insurance Medicine, Basel, Switzerland

7. Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

ABSTRACT

Background: The purpose of the present study was to perform a systematic review and meta-analysis of the use of alternative antibiotic regimens—including (A) antibiotic prophylaxis versus no prophylaxis, (B) longer versus shorter duration of antibiotic prophylaxis, and (C) alternative drugs—for patients with open fracture of the extremities.

Methods: Data sources included CINAHL, EMBASE, MEDLINE, the Cochrane Central Registry of Controlled Trials (CENTRAL), and the Cochrane database of systematic reviews from 1965 to December 2013. All randomized controlled trials comparing the effectiveness of antibiotic prophylaxis in patients with open fracture of the extremities were eligible.

Results: We identified 329 potentially eligible articles, of which seventeen proved to be eligible. In four randomized controlled trials involving 472 patients, we found a significantly lower infection rate in patients receiving antibiotic prophylaxis compared with those not receiving antibiotic prophylaxis (risk ratio = 0.37 [95% confidence interval, 0.21 to 0.66]; absolute risk reduction=9.6% [95%confidence interval, 5.2% to 12.1%]). In three studies involving 1104 patients, we found no difference in the infection rate when a longer duration of antibiotics (three to five days) was compared with a shorter duration (one day) (risk ratio = 0.97; 95% confidence interval, 0.69 to 1.37). Confidence in the estimates for both questions was low to moderate. Individual comparisons of alternative drugs yielded estimates warranting only low to very low confidence.

Conclusions: Results of randomized controlled trials performed to date provide evidence that antibiotic prophylaxis reduces subsequent infection and that courses as short as one day are as effective as courses of three to five days, although the evidence warrants only low to moderate confidence. Given current practice, a large, multicenter, low risk of bias, randomized controlled trial enrolling representative populations and addressing the duration of antibiotics may be the next optimum step in investigation.

Key words:

open fracture; antibiotic; prophylaxis; infection; systematic review

Introduction

Open fractures—fractures involving the communication of bone through the skin and with the external environment[1]—are considered to be contaminated wounds. A key issue in treatment is the prevention of infection, which can occur in association with as many as 50% of open fractures. Strategies to minimize infection include copious irrigation, debridement, optimum fracture repair, and administration of antibiotics[2-4].

Despite the implementation of these strategies, bacterial infection remains an important cause of nonunion and osseous instability after open fracture[2]. According to the results of culture of tissues at open fracture sites prior to orthopaedic operations, gram-positive bacteria are most common in association with Gustilo-Anderson type-I fractures[5,6]. The more severe the fracture type (i.e., Gustilo-Anderson type II or III), the more likely that gram-negative or mixed bacteria are present[7].

Given the certainty of contamination and the very high incidence of infection, prophylactic use of antibiotics after open fracture has become routine[8,9]. Depending on the severity of the fracture and the preferences of the treating surgeon, the antibiotic may be given orally, parenterally, or locally. Surgeons frequently use multiple antibiotics to decrease the risk of resistance and to increase efficacy[10]. Some authorities have recommended that patients with open fractures of the extremities should receive intravenous antibiotics as prophylaxis against infection as early as possible, preferably within three hours after the injury[9,11-13]. Commonly recommended regimens include first or

second-generation cephalosporins or, if the patient has an allergy to such agents, clindamycin[11-14].

However, debate continues with regard to the duration of use, the route of administration, and the choice of antibiotics. Therefore, we undertook a systematic review and meta-analysis of the available evidence from randomized controlled trials to assess (A) the impact of antibiotic prophylaxis versus no prophylaxis on the rate of infection, (B) the impact of longer versus shorter duration of antibiotic prophylaxis on the rate of infection, and (C) the impact of alternative antibiotics on the rate of infection.

Materials and Methods

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[15] for reporting systemic reviews (Fig. 1).

Eligibility Criteria

We included randomized clinical trials in which (1) the patients had presented with one or more open fractures involving the arms and legs, (2) an antibiotic prophylactic regimen was compared with any other regimen or with no antibiotic prophylaxis, and (3) the incidence of postoperative infection was reported as one of the clinical outcomes. We excluded studies addressing the use of antibiotics in patients with known infections; studies of patients with fractures involving the fingers or toes; and studies restricted to patients with gunshot wounds, injuries from bomb explosions, or HIV/AIDS (human immunodeficiency virus/acquired immune deficiency syndrome).

Data Sources and Search Strategy

We searched CINAHL, EMBASE, MEDLINE, the Cochrane Central Registry of Controlled Trials (CENTRAL), and the Cochrane database of systematic reviews from 1965 to December 2013. We restricted the search to human participants. Keywords included antibiotics, antimicrobial, antibiotic prophylaxis, open fracture, compound fracture, Gustilo- Anderson type, fracture fixation, nonunion, infection, and the names of specific antibiotics (see Appendix 1). An expert librarian (N.B.) developed the search strategy for our systematic review. One can

retrieve the same search results in our study by entering in the MEDLINE search engine all of the commands listed in the Appendix 1 and by using the translated approach with the same keywords and logic from the Appendix 1 in other literature databases listed above[16].

Study Selection and Data Abstraction

Reviewers, working in pairs, independently screened titles and available abstracts of identified citations and adjudicated the eligibility of the full text of titles and abstracts that were judged to be potentially eligible.

Using a data abstraction form created with Microsoft Excel, teams of reviewers, working in pairs, extracted the following data independently from each eligible study: funding and country of study; duration of follow-up; population characteristics, including sex distribution and age; sites and Gustilo-Anderson types of open fractures[5,6] in terms of both numbers and proportions; intervention data, including antibiotic prophylaxis intervention details (antibiotic drug, dose, route of administration, start time, duration) and fluid irrigation type; and outcome data, including the number and proportion of infections in each study group and the risk ratio (RR) and its 95% confidence interval (CI).

Risk of Bias and Confidence in Effect Assessment

Using a modified version of the Cochrane risk of bias tool[17,18], teams of reviewers, working in pairs, independently assessed seven domains: (1) adequacy of sequence generation; (2) allocation concealment; (3) blinding of participants,

health-care professionals, data collectors, and data analysts; (4) blinding of outcome assessors; (5) incomplete outcome data; (6) selective outcome reporting; and (7) other sources of bias. Reviewers chose from response options of "definitely yes," "probably yes," "probably no," and "definitely no" for each of the domains, with "definitely yes" and "probably yes" ultimately assigned a low risk of bias and "definitely no" and "probably no" assigned a high risk of bias[17]. We used the "risk of bias summary" figure function of Review Manager (RevMan [Computer program]. Version 5.2.Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2012) to present the risk of bias result of individual studies from the seven domains of the modified Cochrane risk of bias instrument[17,19]. The RevMan software generates a red dot with a minus mark when we enter "high risk of bias" for a domain in a particular study and a green dot with a plus mark when we enter "low risk of bias."[19] The resulting figure provides a vivid and transparent accounting of the risk of bias for every included study (Fig. 2)[19].

Reviewers resolved disagreements regarding eligibility, data abstraction, or risk of bias through discussion[18].

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology was used to rate confidence in estimates of effect (quality of evidence) as high, moderate, low or very low[18,20]. We used detailed GRADE guidance to assess overall risk of bias[18,21], imprecision[18,22], inconsistency[18,23], indirectness[18,24] and publication bias[18,25] and summarized results in an evidence profile[18,26]. In terms of the risk of bias

across studies, there are no serious limitations when most information comes from studies at low risk of bias and we therefore do not rate down for risk of bias. There are serious limitations when most information comes from studies at moderate or high risk of bias and under these circumstances we rate down one level in the extent of risk of bias[21]. Imprecision relates to the 95% CI around the effect difference between the two groups being compared, with consideration of effect size and sample size[22]. Quality of a body of evidence may vary from high (four plus ⊕ ⊕ ⊕ ⊕), moderate (three plus ⊕ ⊕ ⊕ ○), low (two plus ⊕ ⊕ ○ ○) to very low (one plus ⊕ ○ ○ ○), depending on the overall rating of the studies included in themetaanalysis[27]. We included as footnotes detailed explanations of our judgments in the GRADE evidence profile[26].

Data Synthesis and Statistical Alalysis

We assessed chance-corrected agreement in full text eligibility judgments and risk of bias assessments using the Kappa statistic[28]. We calculated pooled RRs and associated 95% CIs for infection using random effects models applying the Mantel-Haenszel (M-H) method[29]. We calculated the risk difference and 95% confidence intervals on the basis of the values of the baseline risk and the risk ratio[18,19]. Specifically, we use the median infection rate of the control groups as the baseline risks. In the case of four studies, the median was the average of the rates in themiddle two studies. The heterogeneity among the studieswas assessed with the I^2 statistic[19]. Analyses were performed using RevMan version 5.2.

Results

Study Identification

Our search identified 13,499 abstracts from the electronic database search, of which 1,155 were excluded as duplicates and an additional 11,972 excluded on the basis of review of the title and abstract (Fig. 1). We were unable to access the full text of forty-three articles that had been deemed potentially eligible on the basis of a review of the title and abstract. Of the 329 articles for which the full text was reviewed, 276 were not randomized controlled trials and thirty-six did not assess open fractures involving the extremities, leaving seventeen eligible randomized controlled trials (Fig. 1) [30-46].

The agreement regarding full text eligibility selection was excellent (kappa 0.72), and the agreement in risk of bias assessments near perfect (kappa values from 0.85 to 1.0).

These studies allowed us to compare (A) antibiotic prophylaxis versus no prophylaxis, (B) longer versus shorter duration of antibiotic prophylaxis, and (C) miscellaneous antibiotic regimens (Table I).

A) Antibiotic Prophylaxis versus No Prophylaxis

Four RCTs enrolling 472 patients addressed fracture site infection with and without antibiotic prophylaxis[30-33]. Interventions included penicillins and first-generation cephalosporin administered intravenously. In two studies the patients in the control groups were given no antibiotic prophylaxis and the patients in the intervention groups received antibiotics parenterally for 5

days[30,32]. In two studies the patients in the control group received placebo[31,33], the patients in the intervention group received intravenous antibiotics for 2 days[31] or intravenous antibiotics for 4 days followed by 6 days oral antibiotics[33]. We found that in all 4 trials, randomization sequence generation and blinding of outcome assessment suffered from high risk of bias[17,30-33]. 3 out of 4 trials had high risk of bias on allocation concealment[17,30,32,33]. Risk of bias was also high because of lack of blinding of participants and health care providers in 2 out of 4 trials[17,30,32] (Fig. 2).

Results suggested a large, consistent reduction in infection risk with antibiotic use (RR = 0.37 [95% CI, 0.21 to 0.66], I^2 = 0%) (Fig. 3), resulting in a risk difference of 9.6% fewer (95% CI, 5.2% to 12.1% fewer) infections in the antibiotic prophylaxis groups than the comparator groups. We rated the confidence in the estimates as low to moderate because of risk of bias and imprecision (Table II) [21-27].We rated down imprecision not because of the width of the confidence interval but rather because of the small number of events, resulting in a failure to meet optimum information size criteria[22].

B) Longer versus Shorter Duration of Antibiotic Prophylaxis

Three randomized controlled trials enrolling 1104 patients were included in the meta-analysis comparing the rates of infection after longer-duration (three to five days) and shorter-duration (one day) prophylactic antibiotic use[34-36]. Interventions included first or second-generation cephalosporin given continuously for three to five days[34-36]. Controls included single-dose

cephalosporin[34], double-dose cephalosporin[34], and one day[35] of second-generation cephalosporin or single-dose fluoroquinolone[36]. In all three studies, we judged allocation concealment and the lack of blinding of outcome assessment as having a high risk of bias[17,34-36]. Randomization sequence generation (two of three trials)[17,34,35] and selective reporting (one of three trials)[17,35] were also judged as having a high risk of bias. The risk was low for attrition, reporting, and other bias[17,34-36] (Fig. 2).

Result showed very similar rates of infection between groups receiving three to five days and one day of antibiotics (RR 0.97, 95% CI 0.69-1.37), I^2 =0% (Fig. 4). We rated the quality of evidence as low to moderate because of the risk of bias and imprecision (Table II)[21-27].

C) Individual comparisons of Antibiotic Regimens

Ten RCTs with a sample size varied from 46 to 301 patients compared infection rates for different regimens[37-46].

The risk of bias in individual studies was generally high, mainly because of inadequate sequence allocation, lack of allocation concealment, and lack of blinding (Fig. 2). The risk of bias was high in all studies[17,37-44] except for those of Johnson et al.[17,45] and Moehring et al.[17,46], which had a moderate risk of bias. Studies compared a variety of different regimens; confidence intervals in most studies were verywide[37-46] (Table I).

Two of the ten studies demonstrated significant differences between antibiotic treatments[38,39]. Vasenius et al. reported that patients in the clindamycin group

had a lower infection rate than patients in the cloxacillin group (RR = 0.46 [95% CI, 0.24 to 0.91]) [38]. Waikakul et al. showed that patients in the ofloxacin group had a higher infection rate than patients in the dicloxacillin group (RR = 0.19 [95% CI, 0.04 to 0.77]) [39].We rated confidence in the estimates in all studies as low or very low because of the risk of bias and imprecision[21-25,27,37-46].

Discussion

Results from four randomized controlled trials30-33 enrolling a total of 472 patients suggested large reductions in the relative risk (RR = 0.37 [95% CI, 0.21 to 0.66]) and absolute risk (9.6% [95% CI,5%to 12%]) of infection with antibiotic prophylaxis versus no prophylaxis, although the results warrant only low to moderate confidence due to limitations of risk of bias (Fig. 2) and small total sample size and number of events (Fig. 3, Table II). A meta-analysis of three studies[34-36] enrolling 1104 patients suggested no difference in the infection rate when a longer duration of antibiotics (three to five days) was compared with a shorter duration (one day) (RR = 0.97 [95% CI, 0.69 to 1.37]), although confidence again was low to moderate because of the risk of bias (Fig. 2) and wide confidence intervals (Fig. 4, Table II). Individual comparisons[37-46] all were associated with low or very low confidence in the estimates of effect because of the risk of bias (Fig. 2) and imprecision.

The strengths of the present study include explicit eligibility criteria, a comprehensive search for relevant randomized controlled trials in all languages, duplicate assessments of eligibility and risk of bias with a high level of agreement, and application of GRADE criteria for confidence in estimates of effect. The weaknesses of the present study are related to limitations in the evidence, including the small number of eligible studies, the relatively small sample size, and the high risk of bias in most studies. These limitations led to our relatively low ratings of confidence in the estimates. Among the studies[34-36] pooled in Figure 4, the unit of analysis differs, with two of the studies[35,36] comparing

infection rates of longer versus shorter durations of antibiotic prophylaxis on the basis of the number of patients and with the other study using the number of fractures[34].We contacted the first author of the latter study to obtain the number of infection events using patients as the unit of analysis. However, the original data for that study were not retrievable.We did not exclude that study inthepooled result because, with the small number of events, the difference of using either fractures or patients as the unit would not have altered our result.

Our finding regarding the infection-preventing effect of using antibiotic prophylaxis for patients with open fractures is consistent with the findings of previous systematic reviews[14,47-49]. Gosselin et al., in an analysis of eight studies involving 1106 participants, found that antibiotics protected patients from early infection when compared with no antibiotics or placebo (RR = 0.43 [95% CI, 0.29 to 0.65]) [14]. Our study included fewer randomized controlled trials than did the study by Gosselin et al. because we excluded studies involving fractures of the fingers and gunshot wounds. We excluded studies of finger fractures because the prognosis following such fractures differs from that following extremity fractures. For finger fractures, the anatomy of the hand is such that, if an infection occurs, the infection may track down the tendon sheath[50]. For gunshot wounds, optimum management may vary depending on whether the gun was a high-velocity weapon, a low-velocity weapon, or a shotgun, each of which carries its own prognosis[51].

Other systematic reviews have led to the same conclusion that antibiotic prophylaxis has protective effects but have not provided the pooled risk ratios for

the included studies[47-49]. To our knowledge, no previous systematic review has compared the effects of different durations of antibiotic prophylaxis or different antibiotic regimens. Also, to our knowledge, no previous review has used synthetic approaches such as GRADE to assess the quality of evidence[27,52].

The low confidence in the effect of prophylaxis, despite the apparently large effect, suggests that the conduct of additional large studies with designs ensuring low risk of bias would be desirable. The long-established consensus in the community in favor of antibiotics would likely make such a trial unfeasible in the current environment. Our results suggest, however, that a single day's exposure to antibiotics is similar in its effects to more prolonged administration. An initial trial comparing shorter and longer regimens might well be feasible, and, if it showed no difference, the climate of opinion regarding the possibility of a trial of antibiotics versus no antibiotics could possibly change.

Aside from the issues of whether antibiotics should be administered at all and the duration of their use, other issues, including the optimum choice of antibiotic, the route of administration, and the optimum start time, remain unresolved. It is also possible that different regimens and durations may be preferable for different patients according to the site and severity of the fractures. Previous in vitro and in vivo experimental studies in both animals and humans showed negative effects of topical antibiotics (in the form of impregnated beads or cements in clinical practice) on bone cell function and fracture repair. High concentrations of most antibiotics can inhibit bone-healing by affecting chondrocytes and osteoblasts and increasing mineralization of bone. The optimum dose of topical antibiotics to

prevent infection without negative effects on bone repair is unknown[53].

Resolution of these issues will require randomized trials of superior design to those undertaken to date. Such studies should address the limitations of previous studies, including the failure to document adverse reactions to antibiotics and the nature of the infections that occur (e.g., superficial or deep). In addition, they should be large, multicenter studies that are sufficiently powered to provide definitive results. Finally, they should implement strategies to reduce the risk of bias (including concealed allocation and blinding of patients, clinicians, and those involved in outcome assessment) as well as strategies to minimize loss to follow-up.

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Conflict of Interest

No conflict declared.

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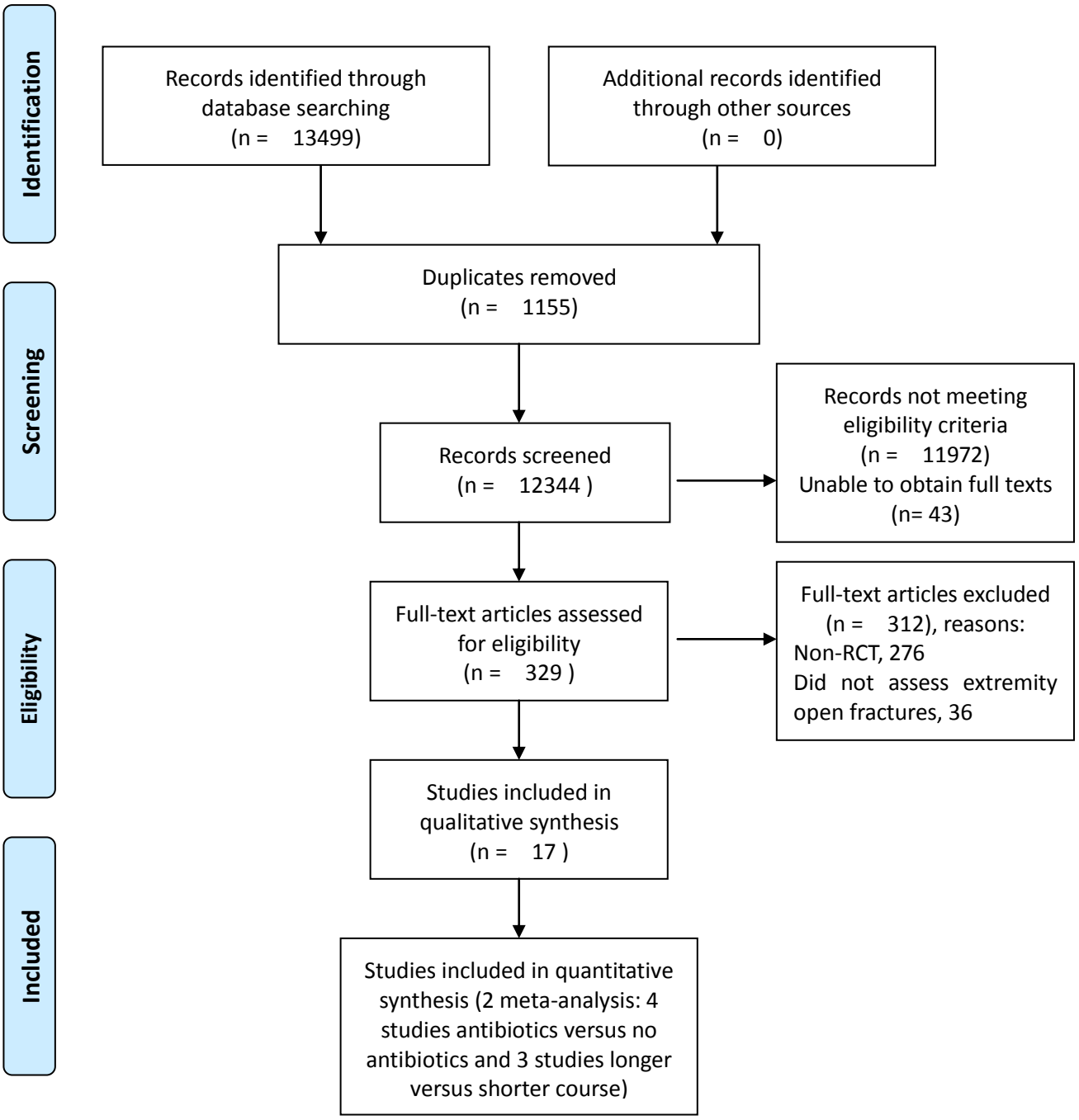

Fig. 1

Eligibility assessment flow diagram according to PRISMA guidelines

(doi:10.1371/journal.pmed1000097). RCT = randomized controlled trial.

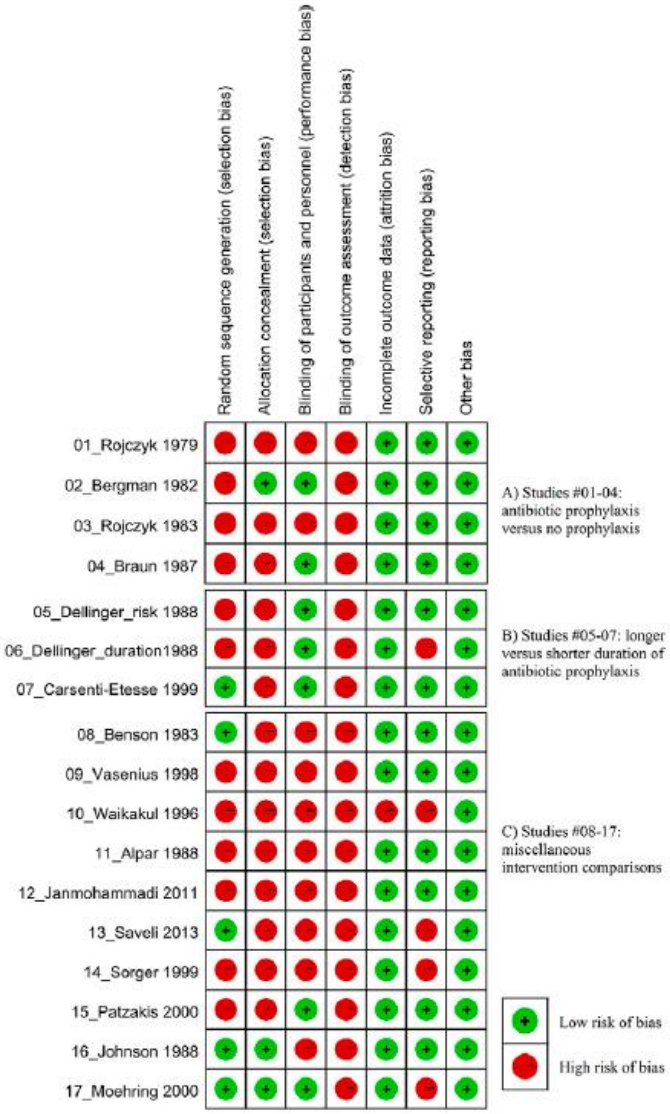

Fig. 2
Risk of bias in the individual studies included. The seventeen studies are listed on the left side of each row. The seven domains for risk of bias assessment of an individual study are shown at the top of each column. A red dot indicates a high risk of bias. A green dot indicates a low risk of bias.

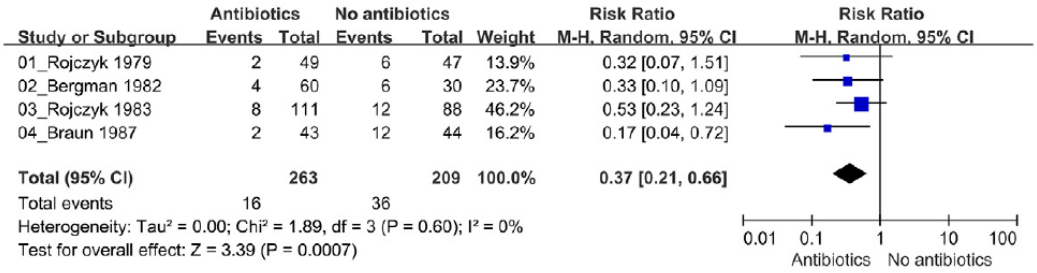

Fig. 3

Forest plot showing fracture site infection with antibiotic prophylaxis versus no antibiotic prophylaxis. Blue squares indicate the risk ratio (RR); values of <1.0 indicate that antibiotic prophylaxis was associated with decreased hazard (that is, fewer infections). Horizontal lines indicate the 95% confidence intervals (CIs). The width of the CI indicates the precision of the estimate: the greater the width, the less precise the estimate. CIs that do not include 1 indicate a significant difference. The central vertical line indicates no effect of the intervention (RR = 1). The center and tips of the diamond indicate the combined point estimate (risk ratio) and CI for the meta-analysis. df = degrees of freedom.

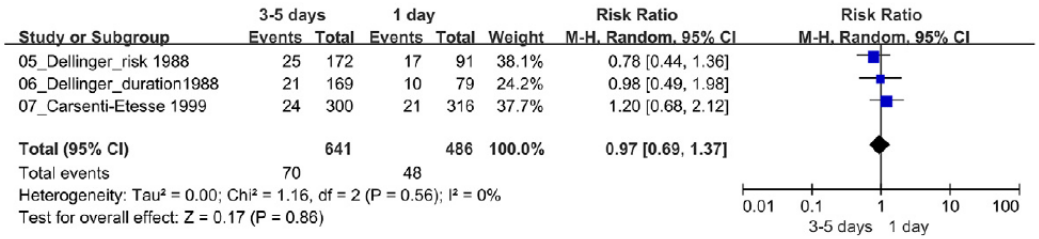

Fig. 4

Forest plot showing fracture site infection with three to five days versus one day of antibiotic prophylaxis. Because the infection rate based on the numbers of patients was not available after we contacted the first author of the study labeled 05_Dellinger_risk 1988, the unit for that study is given as the number of fractures instead of patients. Blue squares indicate the risk ratio (RR); values of <1.0 indicate that antibiotic prophylaxis was associated with decreased hazard (that is, fewer infections). Values of >1.0 indicate that antibiotic prophylaxis was associated with increased hazard (that is, more infections). Horizontal lines indicate the 95% confidence intervals (CIs). The width of the CI indicates the precision of the estimate; the greater the width, the less precise the estimate. CIs that include 1 indicate that there was no significant difference. The central vertical line indicates no effect of the intervention (RR = 1). The center and tips of the diamond indicate the combined point estimate (risk ratio) and CI for the meta-analysis. df = degrees of freedom.

TABLE I Characteristics of the Eligible Randomized Controlled Trials and Patients in These Studies*

Study Number	Author (Year)	Patient Characteristics	Fracture Site *(no. [%])*	Gustilo-Anderson Type	Intervention†	Comparator†	Infection Rate *(no. [%])*	Chi-Square Test‡
(A) Randomized controlled trials comparing antibiotic prophylaxis to no prophylaxis								
1	Rojczyk and Malottke (1979)[30]	96 patients. Sex distribution and age NR	Upper extremity, 48 (50%). Lower extremity, 48 (50%)	Type I, 28 (29%). Type II, 43 (45%). Type III, 25 (26%)	Azlocillin (a) IM 3 × 5 g for 5 days. Start time NR	No antibiotics	Intervention group, 2 of 49 (4%; 1 deep, 1 superficial). Control group, 6 of 47 (13%; 4 deep, 2 superficial)	0.32 (0.07 to 1.51)
2	Bergman (1982)[31]	90 patients. Female, 31 (34%). Mean age, 51 yr	Upper extremity, 29 (32%). Lower extremity, 61 (68%)	Type I, 55 (61%). Types II and III, 35 (39%)	Dicloxacillin (b) IV 4 × 2 g for 2 days, or benzylpenicillin (a) IV 4 × 3 million IU for 2 days. Start time within 6 hours after injury and before surgery.	Placebo: saline solution	Intervention group, 4 of 60 (7%; 4 superficial). Control group, 6 of 30 (20%; 2 deep, 4 superficial)	0.33 (0.10 to 1.09)
3	Rojczyk (1983)[32]	199 patients. Female, 49 (25%). Mean age, 30 yr	Upper extremity, 35 (18%). Lower extremity, 164 (82%)	Type I, 62 (31%). Type II, 78 (39%). Type III, 59 (30%)	Azlocillin (a) IM 4 × 1 g for 5 days; for more severely injured patients, used cefazolin (c) instead. Start time NR	No antibiotics	Intervention group, 8 of 111 (7%; 3 deep, 5 superficial). Control group, 12 of 88 (14%; 5 deep, 7 superficial)	0.53 (0.23 to 1.24)
4	Braun et al. (1987)[33]	87 patients with 91 fractures. Female, 34 (39%). Mean age, 42 yr	Upper extremity, 20 fractures (22%). Lower extremity, 71 fractures (78%)	NR	Cloxacillin (b) IV 4 × 1 g for 4 days; thereafter, 4 × 1.5 g cloxacillin (b) orally given for 6 days. Start time within 6 hours after injury and before surgery	Placebo	Intervention group, 2 of 43 (5%). Control group, 12 of 44 (27%)	0.17 (0.04 to 0.72)
(B) Randomized controlled trials comparing 3-5 days versus 1 day of antibiotic prophylaxis								
5	Dellinger et al. _risk (1988)[34]	240 patients with 263 fractures. Sex distribution NR. Median age, 33 yr	Upper extremity, 71 fractures (27%). Lower extremity, 192 fractures (73%)	Type I, 60 (25%). Type II, 112 (47%). Type III, 68 (28%)	Cefazolin (c) or cefamandole (d) IV 4 × 1 g for 3 to 5 days. Start time within 6 hours after injury and before surgery	2 subgroups: Single dose of cefonicid (d) IV 2 g. Two doses of cefamandole (d) IV. Start time within 6 hours after injury and before surgery	Longer-duration group, 25 (15%) of 172 fractures. Shorter-duration group, 17 (19%) of 91 fractures	0.78 (0.44 to 1.36)
6	Dellinger et al. _duration (1988)[35]	248 patients with 264 fractures. Female, 43 (17%). Mean age, 30 yr	NR	Type I, 70 (28%). Type II, 72 (29%). Type III, 106 (43%)	Cefazolin (c) or cefamandole (d) IV 4 × 1 g for 3 to 5 days. Start time within 6 hours after injury and before surgery	Cefonicid (d) IV 2 g for 1 day. Start time within 6 hours after injury and before surgery	Longer-duration group, 21 of 169 (12%; 16 deep, 5 superficial). Shorter-duration group, 10 of 79 (13%; 5 deep, 5 superficial)	0.98 (0.49 to 1.98)
7	Carsenti-Etesse et al. (1999)[36]	616 patients. Sex distribution and age NR	Leg (lower extremity). 616 (100%)	NR	Cefazolin (c) IV 4 × 1 g for 2 days followed by oxacillin (b) orally given 3 × 1 g for 3 days. Start time NR	Single dose of pefloxacin (f) IV 800 mg. Start time NR	Longer-duration group, 24 of 300 (8%). Shorter-duration group, 21 of 316 (7%)	1.20 (0.68 to 2.12)

continued

TABLE I (*continued*)

Study Number	Author (Year)	Patient Characteristics	Fracture Site *(no. [%])*	Gustilo-Anderson Type	Intervention†	Comparator†	Infection Rate *(no. [%])*	Chi-Square Test‡
(C) Miscellaneous comparisons of antibiotic regimens								
8	Benson et al. (1983)[37]	78 patients with 82 fractures. Female, 9 (12%). Mean age, 30 yr	Upper extremity, 31 (40%). Lower extremity, 44 (56%). Both extremities, 3 (4%)	NR	Clindamycin IV for 5 days. Start time within 6 hours after injury and before surgery	Cefazolin (c) IV for 5 days. Start time within 6 hours after injury and before surgery	Clindamycin group, 2 of 34 (6%). Cefazolin group, 3 of 42 (7%). 2 patients received only oral cephalexin (c), no infection occurred	0.82 (0.15 to 4.65)
9	Vasenius et al. (1998)[38]	227 patients with 240 fractures. Female, 80 (35%). Mean age, 38 yr	Upper extremity, 91 fractures (38%). Lower extremity, 149 fractures (62%)	Type I, 60 (26%). Type II, 109 (48%). Type III, 58 (26%)	Clindamycin IV 4 × 300 to 600 mg by patient weight for 3 days. Start time within 6 hours after injury and before surgery	Cloxacillin (a) IV 4 × 2 g for 3 days. Start time within 6 hours after injury and before surgery	Clindamycin group, 11 of 118 (9%; 6 deep, 5 superficial). Cloxacillin group, 22 of 109 (20%; 7 deep, 15 superficial)	0.46 (0.24 to 0.91)
10	Waikakul et al. (1996)[39]	56 patients. Female, 16 (29%). Mean age, 23 yr	Compound fracture of hand (upper extremity), 56 (100%)	Type II, 20 (36%). Type III, 36 (64%)	Ofloxacin (f) orally given 2 × 300 mg for 5 days. Start time NR	Dicloxacillin (b) orally 4 × 1 g for 5 days. Start time NR	Ofloxacin group, 2 of 29 (7%; 2 superficial). Dicloxacillin group, 10 of 27 (37%; 3 deep, 7 superficial)	0.19 (0.04 to 0.77)
11	Alpar (1988)[40]	60 patients. Female, 15 (25%). Mean age, 30.5 yr	Upper extremity, 11 (18%). Lower extremity, 49 (82%)	Type I, 12 (20%). Type II, 20 (33%). Type III, 28 (47%)	Cephradine (c) IM 4 × 1 g until patients could tolerate oral administration, at which point given 2 × 500 mg. The whole duration was a maximum of 10 days. Start time within 6 hours after injury and before surgery	Flucloxacillin (b) IM 4 × 250 mg until patients could tolerate oral administration given the same drug and dose. The whole duration was a maximum of 10 days. Start time within 6 hours after injury and before surgery	Cephradine group, 0 of 30. Flucloxacillin group, 2 of 30 (7%)	0.20 (0.01 to 4.00)
12	Janmohammadi and Hasanjani Roshan (2011)[41]	301 patients. Female, 86 (29%). Mean age, 37 yr	Upper extremity, 69 (23%). Lower extremity, 199 (66%). Both extremities, 33 (11%)	Type IIIA, 301 (100%)	Cefazolin (c) IV 3 × 1 g plus ciprofloxacin (f) orally given 2 × 500 mg for 3 days. Start time NR	Cefazolin (c) IV 3 × 1 g plus gentamicin (g) 5 mg/kg/d in 3 divided doses for 3 days. Start time NR	Intervention group, 10 of 153 (7%). Control group, 8 of 148 (5%)	1.21 (0.49 to 2.98)
13	Saveli et al. (2013)[42]	101 patients. Female, 36 (28%). Mean age, 41 yr	NR	Type I, 43 (43%). Type II, 24 (24%). Type III, 34 (34%).	Cefazolin (c) IV 3 × 1 g (weight <80 kg) or 3 × 2 g (weight ≥80 kg) plus vancomycin IV based on patient glomerular filtration rate, start from presentation to hospital until 24 hours after fracture fixation	Cefazolin (c) IV 3 × 1 g (weight <80 kg) or 3 × 2 g (weight ≥80 kg) start from presentation to ER until 24 hours after fracture fixation	Intervention group, 9 of 48 (19%; 6 deep, 3 superficial). Control group, 8 of 53 (15%; 5 deep, 3 superficial)	1.24 (0.52 to 2.96)
14	Sorger et al. (1999)[43]	71 patients with 75 fractures. Female, 25 (35%). Mean age, 36 yr	NR	Type II, 55 fractures (73%). Type III, 20 fractures (27%)	Once daily, high dose gentamicin (g) IV 6 mg/kg plus cefazolin (c) 3 × 1 g begun in ER and continued for 48 hours after each operation until wound closure	Divided, low-dose gentamicin (g) IV 5 mg/kg/d divided in 2 daily doses plus cefazolin (c) 3 × 1 g begun in ER and continued for 48 hours after each operation until wound closure	Intervention group, 2 of 30 (7%). Control group, 6 of 41 (15%)	0.46 (0.10 to 2.10)

continued

TABLE I (*continued*)

Study Number	Author (Year)	Patient Characteristics	Fracture Site *(no. [%])*	Gustilo-Anderson Type	Intervention†	Comparator†	Infection Rate *(no. [%])*	Chi-Square Test‡
15	Patzakis et al. (2000)[44]	163 patients with 171 fractures. Female, 29 (18%). Median age, 30 yr	Upper extremity, 60 fractures (35%). Lower extremity, 111 fractures (65%)	Type I, 65 fractures (38%). Type II, 54 fractures (32%). Type III, 52 fractures (30%)	Ciprofloxacin (f) IV 2 × 400 mg and orally given 2 × 500 mg after surgical irrigation and debridement. The whole duration was from 3 days (1 surgical procedure) to a maximum of 8 days (more than 1 surgical procedure). Start time within 6 hours after injury and before surgery	Cefamandole (d) IV 4 × 2 g, gentamicin (g) IV 3 × 80 mg and placebo in oral phase after surgical irrigation and debridement. The whole duration was from 3 days (1 surgical procedure) to a maximum of 8 days (more than 1 surgical procedure). Start time within 6 hours of injury and before surgery	Ciprofloxacin group, 11 (14%) of 78 fractures. Cefamandole/ gentamicin group, 6 (6%) of 93 fractures.	2.19 (0.85 to 5.64)
16	Johnson et al. (1988)[45]	46 patients. Female, 5 (11%). Mean age, 29 yr	Tibia (lower extremity), 46 (100%)	Type II, 19 (41%). Type III, 27 (59%)	Cefotaxime (e) IV 3 × 1 g for 2 days. Start time within 6 hours after injury and before surgery	Cefazolin (c) IV 3 × 1 g for 2 days. Start time within 6 hours after injury and before surgery	Cefotaxime group, 4 of 21 (19%). Cefazolin group, 6 of 25 (24%)	0.79 (0.26 to 2.44)
16	Johnson et al. (1988)[45]	46 patients. Female, 5 (11%). Mean age, 29 yr	Tibia (lower extremity), 46 (100%)	Type II, 19 (41%). Type III, 27 (59%)	Cefotaxime (e) IV 3 × 1 g for 2 days. Start time within 6 hours after injury and before surgery	Cefazolin (c) IV 3 × 1 g for 2 days. Start time within 6 hours after injury and before surgery	Cefotaxime group, 4 of 21 (19%). Cefazolin group, 6 of 25 (24%)	0.79 (0.26 to 2.44)
17	Moehring et al. (2000)[46]	67 patients with 75 fractures. Female, 17 (25%). Mean age, 34 yr	Upper extremity, 5 fractures (7%). Lower extremity, 70 fractures (93%)	NR	Cefazolin (c) IV certain mg/kg weight as recommended (source NR) at admission to ER. Beads group: tobramycin (g) impregnated beads implanted at surgical site, no further antibiotics were given. Beads + antibiotic group: beads implanted and regimen same as with control group	Cefazolin (c) IV certain mg/kg weight as recommended (source NR) at admission to ER. Cefazolin (c) IV 3 × 1 g and where indicated, gentamicin (g) IV 2 × 2.5 mg/kg until wound was closed	Beads group, 2 of 24 fractures in 22 patients (8% by fractures, 9% by patients). Beads + antibiotic group, 2 of 13 fractures in 12 patients (15% by fractures, 17% by patients). Control group, 2 of 38 fractures in 33 patients (5% by fractures, 6% by patients)	1.50 (0.23 to 9.87) for comparison of beads group and control group based on number of patients. 2.75 (0.43 to 17.41) for comparison of beads + antibiotic group and control group based on number of patients.

*NR = not reported, IM = intramuscular, IV = intravenous, and ER = emergency room. †The classification of antibiotics is indicated by a lowercase letter in parentheses as follows: (a) penicillin class or extended spectrum penicillin, (b) penicillinase-resistant penicillin, (c) first-generation cephalosporin, (d) second-generation cephalosporin, (e) third-generation cephalosporin, (f) fluoroquinolone, (g) aminoglycoside. ‡Unless otherwise specified, the data are given as the risk ratio and 95% confidence interval. The online tool MedCalc (www.medcalc.org) was used to calculate these values for all of the studies.

TABLE II GRADE Evidence Profile of Studies of Antibiotic Prophylaxis Among Patients with Open Fractures

No. of Participants (No. of Studies)	Quality Assessment					Summary of Findings			
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect*	Infection Rate in Control Group†	Risk Difference	Confidence in Estimates of Effect
(1) Fracture-site infection with antibiotic prophylaxis versus none									
472 patients (4 randomized controlled trials)	Serious limitations‡	No serious limitations	No serious limitations	Serious limitations§	Not detected	0.37 (0.21 to 0.66)	15.3%	9.6% fewer infections in intervention group (95% CI, 5.2% fewer to 12.1% fewer)	⊕⊕○○ low to moderate due to risk of bias and imprecision
(2) Fracture-site infection with 3-5 days versus 1 day of antibiotic prophylaxis									
1104 patients (3 randomized controlled trials)	Serious limitations#	No serious limitations	No serious limitations	Serious limitations**	Not detected	0.97 (0.69 to 1.37)	12.7%	Difference not significant	⊕⊕○○ LOW to moderate due to risk of bias and imprecision

*The values are given as the risk ratio and the 95% CI. †The median of the event rate of the included studies was used for calculation of risk difference. ‡Serious risk of bias due to poor performance in randomization sequence generation and the lack of blinding of outcome assessment in all four trials, poor performance in allocation concealment in three of four trials, and lack of blinding of participants and personnel in two of four trials. §Serious limitations due to small sample size and number of events. #Serious risk of bias due to allocation concealment and the lack of blinding of outcome assessment in all three trials, poor performance in randomization sequence generation in two of three trials, and selective reporting in one of three trials. **Serious limitations due to wide confidence intervals in the pooled estimates.

Appendix 1. MEDLINE title and abstract search strategy for effects of antibiotic prophylaxis in patients with open fracture

1. antibiotics.mp. or exp Anti-Bacterial Agents/

2. antibiotic prophylaxis.mp. or exp Antibiotic Prophylaxis/

3. (anti-microb* or anti bact* or antibact*).mp.

4. (antibiotic* or antimicrob*).mp.

5. cephalothin.mp.

6. antibioprophylaxis.mp.

7. cloxacillin.mp.

8. exp AMOXICILLIN/ or AMOXICILLIN.mp.

9. exp Ampicillin/ or AMPICILLIN.mp.

10. CLAVULANIC ACID.mp.

11. AMOXICLAV.mp.

12. AUGMENTIN.mp.

13. TICARCILLIN.mp.

14. exp Cephalosporins/ or CEPHALOSPORIN*.mp.

15. (KEFLEX or CEFAMANDOLE or KEFADOL or CEFAZOLIN* or KEFZOL or CEFIXIME or SUPRAX).mp.

16. (CEFOTAXIME or CLAFORAN or CEFOXITIN or MEFOXIN or CEFPIROME or CEFROM or CEFPODOXIME).mp.

17. (ORELOX or CEFPROZIL or CEFZIL or CEFRADINE or VELOSEL or CEFTAZIDIM or ORTUM or KEFADIM).mp.

18. (CEFTRIAXONE or ROCEPHIN or CEFUROXIME or ZINACEF or ZINNAT or CEFONICID or AZTREONAM).mp.

19. (AZACTAM or IMIPENEM or ILASTATIN or PRIMAXIN or MEROPENEM).mp.

20. (TETRACYCLINE* or DETECLO or DEMECLEOCYCLIN or LEDERMYCIN or DOXYCYCLINE or VIBRAMYCIN).mp.

21. (MINOCYCLINE or MINOCINE or OXYTETRACYCLINE or TERRAMYCIN or MACROLIDE*).mp.

22. (ERYTHROMYCIN or ERYMAX or ERYTHROCIN or ERYTHROPED or AZITHROMYCIN or ZITHROMAX).mp.

23. (CLARITHROMYCIN or KLARICID or TELITHROMYCIN or KETEK or TRIMOXAZOLE or SEPTRIN).mp.

24. (TRIMETHOPRIM or MONOTRIM or TRIMOPAN or METRONIDAZOLE or FLAGYL or METROLYL).mp.

25. (PHENOXYMETHYLPENICILLIN or SULFAMETHOXAZOLE or OXACILLIN or CEPHALOTHIN or SULBACTAM).mp.

26. (OFLOXACIN or CLINDAMYCIN or GENTAMYCIN or VANCOMYCIN).mp.

27. (CEFACLOR or DISTACLOR or CEFADROXIL or BAXAN or CEFALEXIN or CEPOREX).mp.

28. (TIMENTIN or FLUCLOXACILLIN or FLUAMPICIL or MAGNAPEN or PIPERACILLIN or TAZOCIN).mp.

29. (streptomycin or cefalotin or dicloxacillin).mp.

30. or/1-29

31. exp fractures, open/

32. (orthopedic adj2 surg*).mp.

33. (open adj9 fracture*).mp.

34. ((open adj2 reduction) and fracture*).mp.

35. (Gustilo or Gustillo).mp.

36. anderson type*.mp.

37. (compound adj9 fracture*).mp.

38. ununited fractures.mp. or exp Fractures, Ununited/

39. fracture fixation.mp. or exp Fracture Fixation/

40. fracture*.mp. or exp Fractures, Bone/

41. (infect$ adj3 (bone$ or fracture$)).mp.

42. ((nonunion or non union) adj9 fracture*).tw.

43. or/31-42

44. 30 and 43

45. animals/ not humans/

46. 44 not 45

CHAPTER 3

Antibiotic Prophylaxis in the Management of Open Fractures:

A Systematic Survey of Current Practice and Recommendations

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Antibiotic prophylaxis in the management of open fractures: a systematic survey of current practice and recommendations

Yaping Chang, MSc[1], Mohit Bhandari, PhD, MD[1,2], Kan Lun Zhu[3], Reza Donald Mirza, MD[3], Melody Ren, MD[4], Sean Alexander Kennedy, MD[5], Ahmed Negm, MD[2], Neera Bhatnagar, MLIS[6], Faysal N Naji, BHSc, MD[7], Lazar Milovanovic, MD[8], Yutong Fei, PhD, MD[9], Arnav Agarwal, BHSc[4], Rakhshan Kamran[1], Sung Min Cho, BHSc[4], Stefan Schandelmaier, MD[1,10], Li Wang, PhD[11,12], Lin Jin, MD[1], Shiyun Hu, PhD, MD[13], Yanping Zhao, PhD[14], Luciane Cruz Lopes, PhD[15], Mei Wang, MSc, MD[1], Brad Petrisor, MD[2], Bill Ristevski, MD[2], Reed A.C. Siemieniuk, MD[1], Gordon H Guyatt, MD[1,3]

Affiliations and Correspondence

1. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, L8S 4K1, Canada

2. Division of Orthopaedic Surgery, Department of Surgery, McMaster University, Hamilton, Ontario, L8S 4K1, Canada

3. Department of Medicine, McMaster University, Hamilton, Ontario, L8S 4K1, Canada

4. Faculty of Medicine, University of Toronto, Toronto, Ontario, M5S 1A8, Canada

5. Department of Diagnostic Radiology, University of Toronto, Toronto, Ontario, M5T 1W7, Canada

6. Health Science Library, McMaster University, Hamilton, Ontario, L8S 4K1, Canada

7. Division of Vascular Surgery, McMaster University, Hamilton, Ontario, L8S 4K1, Canada

8. Department of Medicine, Dalhousie University, Halifax, Nova Scotia, B3H 2Y9, Canada

9. Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, 100029, China

10. Department of Clinical Research, Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel and University of Basel, Switzerland

11. Department of Anesthesia, McMaster University, Hamilton, Ontario, L8S 4K1, Canada

12. Michael G. DeGroote Institute for Pain Research and Care, McMaster University, Hamilton, Ontario, L8S 4K1, Canada

13. Cardiovascular and Cerebrovascular Disease Prevention and Control Research Center of Zhejiang Province, Zhejiang Hospital, Hangzhou, Zhejiang, 310013, China

14. School of Public Health, The University of Hong Kong, Hong Kong, China

15. Pharmaceutical Sciences Postgraduate Course, University of Sorocaba, UNISO, Sorocaba, Sao Paulo, Brazil

ABSTRACT

Background: Evidence regarding antibiotic prophylaxis is limited, and no systematic summary of clinicians' practice, or of expert recommendations, is available. We therefore conducted a systematic survey addressing current practice and recommendations.

Methods: We included publications from January 2007 to June 2017 that addressed antibiotic prophylaxis for patients with open fractures of the extremities. We searched EMBASE, MEDLINE, CINAHL, CENTRAL and the Cochrane database of systematic reviews for clinical studies and surveys of surgeons; WorldCat for textbooks; and websites for guidelines and institutional protocols.

Results: We identified 223 eligible publications that reported 100 clinical practice patterns and 276 recommendations regarding systemic antibiotic administration, and 3 recommendations regarding local antibiotic administration alone. In practice, most (55.6%) used regimens with both gram-positive and gram-negative coverage, and continued the administration for 2 to 3 days (39.2%). The large majority recommendations (97.1%) had language consistent with a recommendation for prophylactic systemic antibiotics. Most recommendations (73.5%) suggested gram-positive coverage for less severe injuries and administration duration of 3 days or less (half suggested 1 day). For more severe injuries, most recommendations suggested broad antimicrobial coverage (88.6%) continued for 2 to 3 days (60.7%). Most publications reported practice or recommended intravenous administration of antibiotics immediately or within four hours after

injury.

Conclusions: Current practice and recommendations strongly support early systemic antibiotics prophylaxis for patients with open fractures of extremities. Differences in antibiotic regimens, doses and durations of administration remain in both practice and recommendations. Consensus regarding optimal practice will likely require well-designed randomized controlled trials.

KEY WORDS:

open fracture; antibiotic regimen; prophylaxis; practice; recommendation

Introduction

Open fractures are fractures associated with soft tissue compromise that result in a communication of the fracture ends with the outside environment. This may be the result of an "inside-out" type injury where the bone has protruded through the skin or by significant disruption of the soft tissue envelope resulting in skin and soft tissue compromise as can be seen in high energy or other crush type injuries. [1-3]. The Gustilo classification has been the most widely used system for classification of infection risk associated with fracture severity. The system takes into consideration of the energy of the fracture, soft tissue damage, and the degree of contamination. The Gustilo system was modified in 1984 to allow for consideration of more severe injuries (i.e., Type 3 injuries) [4].

In open fractures, there is communication of the fracture site with the outside environment [5]. This communication can result in infection that may not only contribute to wound healing problems, but also play a significant role in the subsequent development of nonunion and continued bony instability [1,2,6,7]. Preventing infection is therefore of utmost importance in open fracture management.

Investigations addressing which bacteria are commonly found in open fracture wounds prior to irrigation and debridement have most frequently identified gram-positive bacteria, such as *Streptococcus spp.* and *Staphylococcus spp.* in Gustilo type 1 and 2 fractures. With increasing severity of open fracture, and with soil-contaminated wounds, gram-negative or mixed bacteria are likely to be present. Clinicians should consider using broader coverage in open fractures

contaminated by fresh water (aeromonas and peudomas) and salt water (vibrio). [2,8]. The association between Gustilo classification and the organisms that colonize wounds may have implications for optimal choice of antibiotics, which is the issue of concern in this article.

Surgeons can use a number of strategies to minimize the development of infection, including timely wound irrigation and debridement, fracture stabilization and the early administration of systemic antibiotics [7,9,10]. Given the certainty of contamination and the high incidence of infection [5], prophylactic use of antibiotics in open fracture care delivered as early as possible after injury has become routine [11,12]. The individual treating surgeon or emergency room doctor typically choose the type of antibiotic, route of delivery and duration. The antibiotic administration may differ depending on department protocols and individual treating surgeons' preferences. Clinicians often use multiple antibiotics together when there is substantial risk that a single agent would not provide antimicrobial coverage against all infecting organisms [13-17].

Given these considerations, a variety of antibiotic regimens are reasonable; the optimal regimen is probably context dependent. Systematic reviews of randomized controlled trials (RCTs) are available and have established that there is moderate quality evidence that antibiotics versus no antibiotics do appreciably reduce wound infections [18,19]. The evidence comes from relatively old studies, and no RCTs have effectively addressed issues such as the optimal choice of antibiotics, whether that choice differs with fracture type, or the optimal duration of antibiotic administration.

Under these circumstances, guidelines become important, and clinicians need to understand the nature and range of advice that guidelines provide. No systematic survey of the antibiotics prophylaxis currently in use or recommended exists to inform practice or future research. We therefore undertook a systematic survey with the goal of summarizing current practice and expert guidance in the use of antibiotics prophylaxis for open fractures. The current article is thus not intended as a systematic review of evidence bearing on use of antibiotics. Rather, it is intended as a systematic survey of reports of surgeons' practice in the use of prophylactic antibiotics, and a complementary systematic survey of the available expert recommendations. The scope includes all published articles that describe practice, and all published articles, textbooks, guidelines and institutional protocols that offer recommendations regarding antibiotic prophylaxis.

Materials and Methods

We registered our study protocol with PROSPERO (Prospective Register of Ongoing Systematic Reviews; identifier: CRD42016053285) and reported results according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) recommendations (Fig. 1) [20].

Eligibility Criteria

We included publications over the last decade that include a section addressing either or both of the two questions: (1) what regimens (drug, dose, route of administration, start time and duration) are clinicians using as prophylaxis and (2) what regimens are experts recommending.

We searched and retrieved the evidence from the following publications: (1) multi-center or single-center RCTs, cohort studies, case-control studies and single arm studies (including case series) that indicate use of antibiotic prophylaxis among patients with open fracture, published from January 1, 2007 to June 30, 2017, and with 80% or more patients enrolled after December 31, 2006; (2) review articles of the management of open fractures that provide guidance regarding appropriate prophylactic antibiotic regimens; (3) surveys of surgeons with information regarding use of antibiotic prophylaxis in open fracture management; (4) orthopedic textbooks with sections on the management of open fractures; (5) clinical practice guidelines addressing the management of open fractures that provide guidance regarding appropriate prophylactic antibiotic regimens; and (6) institutional protocols provided on websites of trauma centers,

published from January 1, 2007 to June 30, 2017.

We excluded publications addressing the use of antibiotics in patients with known infections or HIV/AIDS (human immunodeficiency virus/acquired immune deficiency syndrome) and publications restricted to pediatric injuries.

Data Sources and Search Strategy

We identified relevant publications using a systematic search of EMBASE, MEDLINE, CINAHL, the Cochrane Central Registry of Controlled Trials (CENTRAL) and Cochrane database of systematic reviews. Keywords included antibiotics, antimicrobial, antibiotic prophylaxis, open fracture, compound fracture, Gustilo-Anderson type, fracture fixation, nonunion, infection, and the names of specific antibiotics (Appendix 1). A librarian (N.B.) developed the search strategy. One can retrieve the same search results in our study by entering in the MEDLINE search engine all of the commands listed in the Appendix 1 and by using the modified approach with the same keywords and logic from the Appendix 1 in other literature databases listed above [21]. We also checked the citations and references of the included articles for any additional eligible studies.

We conducted a search for textbooks using WorldCat (the world's largest online catalogue for textbooks, www.worldcat.org). Keywords included orthopedic surgery, orthop(a)edic operation, open fracture, antibiotic prophylaxis and infection prevention, and published from 2007 to 2017. We restricted the search to non-fiction publications. We borrowed the eligible textbooks from Health Sciences Library of McMaster University, The University of Hong Kong,

and other universities across Canada via RACER (Rapid Access to Collections by Electronic Requesting) system. In addition, we checked the references of relevant sections in these textbooks for any eligible publications. We used the latest version of a textbook when more than one version was available.

We consulted the Canadian surgeons (M.B., B.P., B.R. and A.N.) and their international orthopedic colleagues about sources of clinical practice guidelines and internet published protocols addressing the management of open fractures. We conducted open-ended Google search with keywords: trauma, injury, open fracture, antibiotic, and (guideline or protocol). We searched websites of the US National Guideline Clearing House (www.guideline.gov), American Academy of Orthopaedic Surgeons (www.aaos.org), Orthopaedic Trauma Association (www.ota.org), the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk), the National Institute for Health and Care Excellence (NICE) (www.nice.org.uk), the British Orthopaedic Association (www.boa.ac.uk), the East Practice Management Guidelines Work Group (www.east.org), the Medscape (www.medscape.com), the SurgWiki (www.surgwiki.com), the Cambridge Orthopaedics (www.cambridgeorthopaedics.com) and the OrthoBullets (www.orthobullets.com) (www.orthobullets.com/trauma/1004/open-fractures-management) for relevant clinical practice guidelines, published from 2007 to 2017. We used the latest version of a guideline if one had more than one version from the same source.

Study Selection and Data Abstraction

Before starting eligibility review, reviewers conducted calibration exercises to ensure consistency. Teams of reviewers (KLZ, RDM, MR, SAK, AN, FN, LM, YF, AA, SMC, RK, SS, LJ, SH, YZ, LCL and BR), working in pairs, independently and in duplicate, screened titles (chapter titles for textbooks) and available abstracts and retrieved the full text of potentially eligible publications. For clinical practice guidelines and institutional protocols, reviewers directly screened full texts. Reviewers resolved disagreement by discussion or, if disagreement remained, through discussion with an arbitrator (G.G. or M.B.).We assessed chance-corrected agreement in full text eligibility judgments using the kappa statistic [22].

We created data abstraction forms with Microsoft Excel. Before starting data abstraction, reviewers conducted calibration exercises to ensure consistency. Reviewers, working in pairs, extracted data independently from each eligible data source. One reviewer extracted data; the other double-checked the results. YC checked all the abstracted data. Abstracted data included the strength of recommendations regarding whether antibiotics should be systematically given to patients with open fractures of extremities, injury severity, prophylactic antibiotic regimen, dose, route of administration, start time, duration and type of evidence.

Data Summarization

We categorized all the included information as a description of practice or a recommendation. Based on the advice of orthopedic surgeons (B.P., M.B., B.R. and A.N.) we combined prognostically similar injury severity groups from the

primary articles, textbook chapters and guidelines. Internal medicine physicians (G.G. and R.A.S.) categorized the prophylactic antibiotic regimens, and resolved disagreements through discussion.

We categorized recommendations regarding whether antibiotics should be given to patients with open fractures as follows: must (i.e., strong in favour), probably should, possibly should, uncertain, probably should not, certainly should not, and no opinion by injury severity groups.

We summarized used or recommended antibiotic regimens. In many instances, authors of both practice and recommendation made statements regarding prophylactic antibiotics, but did not specify the name of drugs or whether they were referring to gram-positive, gram-negative coverage, or both. When we summarized and reported the proportion of antibiotic regimens used or recommended, we did not include in the denominator the reports of practice and recommendations in which authors specified neither drug names nor categories of drugs.

We used Microsoft Excel to record the data and make calculations for sorting and summarization.

Results

Study Identification

Our search identified 17,707 titles and abstracts from the electronic database search, of which 279 were excluded as duplicates and an additional 16,514 were excluded on the bases of review of title and abstract (Fig. 1). We identified 11,691 textbooks from search in the WorldCat website, of which 642 were excluded as duplicates and an additional 10,563 were excluded on the bases of review of title, contents and index (Fig. 1). We were unable to access the full text of four articles and 47 textbooks that had been deemed potentially eligible on basis of a title, abstract, contents or index review.

Of the 910 articles, 439 textbooks and 11 online guidelines that underwent full text review, 754 articles, 377 textbooks and 6 online guidelines did not address prophylactic antibiotics for patients with open fracture of extremities or described evidence after the year of 2006, leaving a total of 223 eligible publications (156 articles, 62 textbook chapters and 5 online guidelines) (Fig. 1).

There was a high-level of agreement for full-text eligibility selection of articles in electronic databases (kappa, 0.80); the agreement regarding full-text eligibility selection of textbooks, clinical practice guidelines and institutional protocols was perfect (kappa, 1.0).

Overall Characteristics of Clinical Practice and Recommendations

Among the 223 included publications, 67 reported actual practice and 147 provided recommendations; 9 reported both practice and recommendations (Table

I, Table II). Three of the 147 recommendations addressed local antibiotic administration alone [23-25].

168 out of the 223 (75.3%) publications were from 2011 or later (Table I). Of the 223 publications, 128 (57.4%) were exclusively or jointly from North America (Table II). We present the absolute numbers in Table III and V.

We reported the number of publications containing information of dose and presented the dose of antibiotics in a descriptive way because the dose in included publications was too diverse to be effectively categorized.

Current practice

Type of publications

Of 76 publications that recorded practice of systemic antibiotic prophylaxis in the treatment of open fractures, 64 (84.2%) were primary clinical studies of single or multiple arms including RCTs, cohort studies, case-control studies, case series and case reports [7,26-88], 3 (3.9%) were surveys completed by surgeons [89-91] and 9 (11.8%) contained both primary data of patients and narrative reviews and hence addressed both practice and recommendations [14-17,92-96].

Systemic antibiotic regimen

The 76 studies included 100 reports of clinical practices by injury severity. Approximately a third reported using only gram-positive coverage (with or without coverage of MRSA or anaerobic coverage), and another 10% only gram-negative coverage (with or without anaerobic coverage) (Table III). The

remainder, just over a half, used regimens covering both gram-positive and gram-negative organisms (Table III).

Thirty-eight publications specified practice in lower extremity injuries (femur [35,43,56,59,60,83,92], tibia [17,28,30,31,35,38-40,44,48,49,51,52,55-57,59,61,62,71,76,78,79,83,84,88,94], ankle [85] and calcaneus [33,34,45]) of varying severity of which 24 specified the antibiotics administered. Two thirds used regimens with broad bacterial coverage and all but one of the others limited coverage to gram-positive organisms [61] (Table V, Appendix 2).

Dose

Nineteen of 100 reports of practice included information regarding dose. Two studies reported either weight-based dosing [95] or empirical administration [83]. The remainder reported use of regimens ranges such as 1-2 g first generation cephalosporin like cefazolin (600-900 mg clindamycin if allergic to cephalosporin) every 6-8 hours or 80-100 mg gentamicin given intravenously (IV) for injuries of various severities [26,40,51,55,56,58,61,62,65,70].

Route of administration

Fifty-six of 100 reports of practice specified that antibiotics were administered IV or IV followed by orally. The remainder did not report route of administration.

Sixteen of 100 reports mentioned that antibiotics were applied locally including, antibiotic-infused equine collagen sponges [37]; nanocrystalline silver dressing [50]; antibiotic-impregnated polymethyl methacrylate (PMMA) beads

[28,31,42,83]; titanium alloy nail with alloy containing antibiotics [39]; impregnated en bloc cement spacer when there was dead space in bones and b-tricalcium phosphate granules coated with bonypid (BonyPidTM) which releases doxycycline at constant rate [93]. The antibiotics impregnated in local carriers were gentamicin, or vancomycin plus tobramycin if cultures were negative culture or not obtained [28,31,37,54,87]; imipenem or amikacin if *Acetinobacter spp.* were isolated [29]. In two studies, the antibiotic regimen was changed to target culture and sensitivity results [29,83].

Time to antibiotic administration

Start time in relation to injury

Of the 100 reports of practice that addressed patients with open fracture of extremities, 38 reported the start time of antibiotic administration in relation to injury. Of these, approximately half gave the regimen immediately, early or as soon as possible after injury, in the emergency room, or administrated on arrival in the emergency department. The remainders administered antibiotics either within one hour, within 2 to 4 hours, or within 10 to 12 hours after the injury. One additional study reported administration within 48 hours (i.e., within 2 days for low velocity ballistic fractures) [89].

Start time in relation to surgery

Seventeen of 100 reports of practice specified start time in relation to surgery. Of these, 17, over half indicated that antibiotics were given pre-operatively

[33,44,56,59,60,78,88], 1 hour [16] or 30 minutes [58] before skin incision. The remainder reported giving antibiotics peri-operatively [27,57], post-operatively [52,71,94], or after the operation [29].

Duration

Fifty-one of 100 reports of practice specified duration of antibiotic administration. One study that investigated 66 surgeons' attitudes toward prophylactic antibiotics reported that most respondents chose single dose [16]. For less severe injuries, Gustilo type 1 and 2 open fractures, approximately a quarter of reports specified antibiotic use for one day [14,63,64], almost half for 2 to 3 days [7,54,66,67,96], and the remainder for 4 to 7 days [86,91] (Table IV). For more severe injuries, Gustilo type 3, of those that reported duration half gave antibiotics for 2 to 3 days, a quarter for 4 to 7 days, and a quarter gave antibiotics for more than 7 days (Table IV). Practice proved similar over time and across continents.

Current recommendations

Type of publications

Of 153 publications (9 of them reported both practice and recommendations) that provided recommendations for systemic antibiotic prophylaxis in the management of open fractures, 61 (39.9%) were textbook chapters [97-157], 15 (9.8%) were clinical practice guidelines [158-172], 70 (45.8%) were review articles [2,3,6,18,92,94,96,174-236], 3 (2.0%) were case series that provided recommendations [17,93,95], and 4 (2.6%) were surveys of surgeons [14-16,173]. Of these 4 surveys, 2

were part A and part B of one study conducted in the USA [14,15]. That study reported that approximately 85% of the 379 respondents suggested initiating antibiotics within 1 hour after identification of an open fracture. Approximately a quarter of the respondents suggested administering antibiotics for at least 72 hours inpatients with a type 3A fracture, another 30% suggested using aminoglycosides in Gustilo type 1 fractures and three quarters suggested aminoglycosides in type 3B fractures [14].

One study was conducted in Nigeria [16]. The authors found that most respondents suggested using the third- and second-generation cephalosporins such as ceftriaxone (46.0%) and cefuroxime (25.0%); 28 of 66 (42.4%) respondents suggested using a single dose of antibiotics within one hour prior to skin incision [16].

Level of recommendations

The 153 eligible publications provided 276 recommendations addressing systemic antibiotic administration by category of injury severity. Of the 276 recommendations, approximately 90% had language consistent with a strong recommendation for prophylactic systemic antibiotics to prevent wound infection irrespective of level of injury severity. For open fractures of the upper and lower extremities, the proportion making a strong recommendation for antibiotics over no antibiotics was approximately 95%. All recommendations for Gustilo type 3, wounds that had come in contact with soil or water, severely contaminated wounds, and high-velocity gun shot wounds or gun shot wounds where velocity

was not specified at all had wording consistent with a strong recommendation in favour of antibiotic prophylaxis (Appendix 3).

Recommended systemic antibiotic regimen

The recommendations for specific antibiotic regimens included 276 recommendations for varying injury severities. For Gustilo type 1 and 2 open fractures, approximately three quarters recommended gram-positive coverage (with or without anaerobic coverage); the remainder recommended regimens that we classified as "broad coverage", including both gram-positive and gram-negative coverage with antibiotics such as carbapenems (e.g., ertapenem, meropenem), piperacillin/tazobactam, third or/and fourth generation cephalosporins (e.g., ceftazidime, ceftriaxone and cefotaxime). For more severe open fractures, most recommendations favoured broad antimicrobial coverage. For open fractures that had come into contact with soil or a marine environment, and/or for severely contaminated wounds, three quarters recommended broad coverage (Table V).

Twenty-eight publications specifically addressed lower extremity injuries (femur [199], knee [200], tibia [94,184,188,193,196,201,205,223], foot and ankle [194,204] and phalanx [206]) and lower in general [3,101,103,107,116,139,140,149,158,164,169,190,208] and made 34 recommendations for various injury severities. Approximately 40% each suggested a broad regimen or limiting coverage to gram-positive organisms (Table V, Appendix 4).

Twenty-two publications addressed gun or combat injury, of which 6

addressed low-velocity gunshot injury [136,216,221,226,227,230], 14 addressed high-velocity gunshot injury [127,136,143,147,168,174,209,210,211,224,226,230], and 2 gun velocity not specified [105,133]. Recommendations were more or less evenly split between gram-positive coverage only and broad coverage (Table V).

Dose

Sixty-six of 276 (23.9%) recommendations offered suggestions regarding antibiotic dosing. Some gave general suggestion regarding dose, such as "adjusted to weight and renal clearance" [95,105,122]. Others provided drug-specific dose recommendations, e.g., IV administration of 1-2 grams of cefazolin every 6-8 hours for Gustilo type 1 and 2 fractures or 600-900 mg clindamycin every 8 hours via IV or 450 mg clindamycin every 4 hours if patients were allergic to cephalosporin or penicillin [104,170], add aminoglycoside 3-5 mg/kg/day for Gustilo type 3 fractures and further add penicillin 2 million units every 4 hours in farm contamination [109,147].

Route of administration

Approximately half of the recommendations did not specify route of administration. Of those that did, almost all recommended IV administration. Approximately a quarter recommended local antibiotics in addition to systemic antibiotics.

Recommendations for local use included delivery of antimicrobials through antibiotic impregnated PMMA beads or bead pouches, PMMA chains, PMMA

strings or PMMA spacers, cement impregnated or mixed with heat-stable powered antibiotics of methylmethacrylate, tobramycin, and/or vancomycin [97-105,181-186]. A typical recommended ratio of antibiotics to cement was 3.6g tobramycin to 40g PMMA [236]. Additional suggestions included BonyPidTM, b-tricalcium phosphate granules coated with bonypid which releases doxycycline at constant rate [94].

Time to antibiotic administration

Time to antibiotic administration in relation to injury

Approximately half of the 276 recommendations made suggestions regarding the optimal time to antibiotic initiation after injury or presentation to hospital. Of these, over half recommended antibiotics to be administrated as soon as/as early as possible after injury or upon arrival to hospital. Of the remainder, most recommended giving antibiotics within three hours of injury.

Time to antibiotic initiation in relation to surgery

Fewer than 10% of the recommendations addressed timing of antibiotic administration in relation to surgery. Of these, two thirds recommended antibiotics be administered one or two hours prior to surgery (before skin incision); a quarter during surgery/peri-operatively [118,172]; and about 10% suggested antibiotic administration post-operatively [94,230].

Duration

Approximately half of the recommendations specified or addressed duration of antibiotic administration. For less severe injuries, Gustilo type 1 and 2 open fractures, half suggested antibiotics for one day or less and the remainder for 2 to 3 days. For Gustilo type 3, approximately 60% suggested 2 to 3 days (some recommendations suggested 72 hours total or 24 hours after wound closure, whichever comes first [117,125,135,169,177]); of the remainder, almost all suggested 4 to 7 days (Table VI).

Recommendations did not differ appreciably by year of publication and or geographic location.

Discussion

We provide a comprehensive overview of actual practice and recommendations for primary antimicrobial prophylaxis in patients with open extremity fractures published over the past 10 years. Recommendations are typically published in textbook chapters, clinical practice guidelines, and review articles.

Information about clinical practice patterns came largely from single arm cohorts and case series, with just a few RCTs and comparative observational studies. Clinicians almost always used broad-spectrum antibiotics rather than antibiotics with only reliable gram-positive coverage, regardless of injury severity (Table III).

The most important difference between recommendations and practice was that, when authors made recommendations for Gustilo 1 or 2 open fractures as a group, they recommended restricting antibiotic use to agents with exclusively gram-positive coverage (Table V). Authors who made recommendations for specific antibiotics to cover gram-positive organisms varied greatly in their suggestions including first and second generation cephalosporins (e.g. example, cefazolin, cephalexin, cefamandole, cefuroxime, cephalexin, or cephradine), as well as anti-staphylococcal penicillins (e.gs., cloxacillin, flucloxacillin, or dicloxacillin), a macrolide (e.g.erythromycin), ampicillin, amoxicillin, and penicillin.

A minority of authors (around one-fifth) suggested, in contrast, broad antimicrobial coverage with activity against both gram-positive and gram-negative organisms with agents such as carbapenems (e.g., ertapenem,

meropenem), piperacillin/tazobactam, third or/and fourth generation cephalosporins (e.g., ceftazidime, ceftriaxone and cefotaxime), beta-lactams with a beta-lactamase inhibitor (e.g., amoxicillin plus clavulinic acid, piperacillin plus tazobactam, or ampicillin plus clavulinic acid), or any combination of antibiotics that included reliable gram-positive and gram-negative coverage for both less and more severe injuries (and were thus more in keeping with practice). All recommendations with available information suggested a duration of 3 days or less (Table V, Table VI).

When authors grouped Gustilo 2 and 3 fractures together, almost all suggested using broad coverage with reliable activity against both gram-positive and gram-negative organisms. This was also true, for wounds with soil or marine contamination (Table V).

Strengths of the present study include explicit eligibility criteria, a comprehensive search for relevant primary clinical studies, review articles including many traditional and grey literature sources, clinical practice guidelines in all languages and duplicate assessment of eligibility with a high level of agreement. This study represents the first systematic survey addressing both what studies report in terms of use of antibiotics in prophylaxis in open fractures, and what experts recommend.

The limitations of our study are primarily related to deficiencies in reporting in the eligible articles. Most included studies in our systematic survey were narrative reviews that made practice recommendations. Recommendations did not provide consistent, comprehensive and detailed description in standard formats

that included drug, dose, route of administration, start time and duration. Details were even more likely to be absent in the reports of experience in clinical practice, observational studies, and RCTs. This is understandable given that antibiotic use was not the focus of these articles.

Our previous systematic review of RCTs addressing the use of antibiotic prophylaxis compared to no prophylaxis suggested that antibiotics reduce the risk of infection, supporting both practice and recommendations. The RCTs that compared prophylaxis to no prophylaxis used antibiotics with gram-positive coverage but no reliable gram-negative coverage (first generation cephalosporins and penicillins). Trials comparing longer and shorter regimens (one day versus three to five days) have failed to demonstrate any benefit with longer durations, based on low to moderate quality evidence. Only single studies have compared different antibiotic regimens and sample sizes have been too small for such studies to be informative. The differences in recommendations regarding which antibiotic to use are therefore understandable – the evidence provides little justification for one regimen or another [18].

Several key questions remain unresolved regarding primary prophylaxis with antibiotics in patients with open fractures. Whether there is any benefit, and if so in what situations, of broad versus targeted antimicrobial coverage, or of coverage for specific pathogens like methicillin-resistant *Staphylococcus aureus* (MRSA) or pseudomonas remains uncertain. This is also the case for whether administration can wait until after obtaining reliable cultures, or the results of such cultures, and for the optimal duration, of prophylaxis. The use of broad

spectrum antibiotics and antibiotics for longer durations comes with notable harms to the patient (adverse effects) and to society (antimicrobial resistance in the community – an increasing concern globally).

Resolution of these issues – in particular the degree of coverage required - will require well-designed RCTs. Such studies should address the limitations of previous studies by ensuring concealed randomization, blinding, complete follow-up, documentation of adverse reactions to antibiotics, and describing the nature of the infections that occur (e.g., superficial or deep). Providing definitive guidance will also require that the trials be large, multicenter studies sufficiently powered to provide definitive results that are broadly applicable. In the interim, clinicians can attend to the guidance offered, being aware that there is disagreement and the current best available evidence does not clearly support any particular approach.

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CONFLICT OF INTEREST

No conflict declared.

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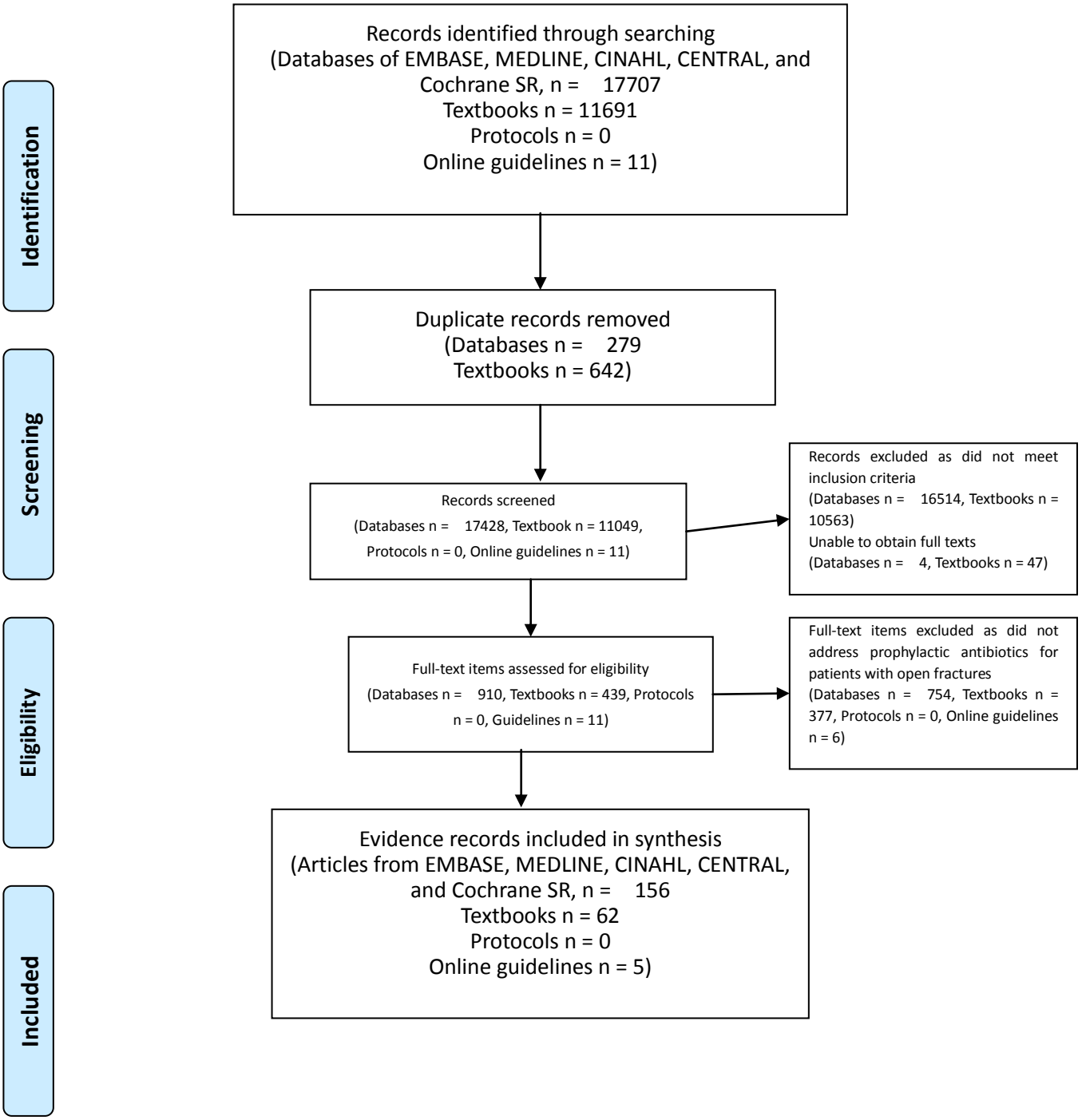

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Table I. Distribution of publications on prophylactic antibiotics to patients with open fractures of extremities in terms of year of publication

Year	Total		Practice		Practice and Recommendation		Recommendation	
	n	(%)	n	(%)	n	(%)	n	(%)
2007	11	4.9	2	3.0			9	6.1
2008	14	6.3					14	9.5
2009	15	6.7	2	3.0	1	11.1	12	8.2
2010	15	6.7	6	9.0			9	6.1
2011	30	13.5	11	16.4			19	12.9
2012	23	10.3	5	7.5			18	12.2
2013	30	13.5	11	16.4	1	11.1	18	12.2
2014	37	16.6	12	17.9	5	55.6	20	13.6
2015	23	10.3	9	13.4	2	22.2	12	8.2
2016	19	8.5	9	13.4			10	6.8
2017	6	2.7					6	4.1
Total	223	100	67	100	9	100	147	100

Table II. Distribution of publications on prophylactic antibiotics to patients with open fractures of extremities in terms of location of publication

Continent	Total		Practice		Practice and Recommendation		Recommendation	
	n	(%)	n	(%)	n	(%)	n	(%)
North America	117	52.5	25	37.3	5	55.6	87	59.2
Europe	63	28.3	17	25.4	2	22.2	44	29.9
Asia	23	10.3	17	25.4			6	4.1
Africa	6	2.7	4	6	1	11.1	1	0.7
Oceania	1	0.4	1	1.5				
Multiple continents	13	5.8	3*	4.5	1†	11.1	9§	6.1
Total	223	100	67	100	9	100	147	100

Notes:

* One study was conducted in North America and Europe. One study was conducted in North America and Asia. One study was conducted in North America and Oceania.

† One study was conducted in North America and Asia.

§ Five evidence records were written by authors from North America and Europe. One was written by authors from North America and Oceania. One was written by authors from Europe and Oceania. One was written by authors from Europe and Asia. One was written be authors from North America, Europe and Asia.

Table III. Regimen in practice of prophylactic antibiotics systematically given to patients with open fractures of extremities*

	Injury severity not specified or for all levels		Gustilo type 1 and 2		Gustilo type 2 and 3		Gustilo type 3		Upper extremity†		Lower extremity§		Soil, manne or severely contaminated wounds		Gun low-velocity		Gun high-velocity	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Antibiotic regimen in practice¶																		
Gram-positive coverage **	2	16.7	3	17.6			1	5.0	2	40.0	7	18.4						
Gram-positive + anaerobic coverage ††	1	8.3	4	23.5			2	10.0					1	50.0				
Gram-positive + MRSA coverage§§													1	50.0			1	33.3
Gram-negative coverage ¶¶			3	17.6			3	15.0										
Gram-negative + anaerobic coverage											1	2.6						
Broad coverage***	1	8.3	7	41.2	2	100	7	35.0			12	31.6					1	33.3
Broad + anaerobic coverage							3	15.0	1	20.0	2	5.3						
Broad + MRSA coverage	1	8.3																
Broad + MRSA + anaerobic coverage											2	5.3			1	100		
Drug name not specified	7	58.3					4	20.0	2	40.0	14	36.8					1	33.3
Total	12	100	17	100	2	100	20	100	5	100	38	100	2	100	1	100	3	100

MRSA, methicillin-resistant Staphylococcus aureus

Notes:
* "Practice" was abstracted from multi-center or single-center randomized controlled trials (RCTs), cohort studies, case-control studies, single arm studies (including case series) and surveys of surgeons that indicate use of antibiotic prophylaxis among open fracture patients.
† Upper extremity fractures include open fractures of hand, radius and fingers, for all Gustilo types of injury severity.
§ Lower extremity fractures include open fractures of tibia, femur, ankle and calcaneus, for all Gustilo types of injury severity.
¶ Clindamycin was used in patients with beta-lactam/penicillin allergies.
** Gram-positive coverage includes first and second generation cephalosporins (e.g., cefazolin, cephalexin, cefacidal, cefadroxil and cefuroxime), macrolide, ampicillin or augmentin, amoxicillin or co-amoxiclav, penicillin and any combination of these drugs.
†† Anaerobic coverage includes metronidazole (flagyl), clindamycin, beta-lactam/beta-lactamase inhibitors (e.g., ampicillin/sulbactam, piperacillin/tazobactam), and carbapenems.
§ § MRSA coverage includes vancomycin or teicoplanin.
¶¶ Gram-negative coverage, in this case, refers to aminoglycosides (e.g., gentamicin, tobramycin and amikacin).
*** "Broad" means broad-spectrum antibiotic coverage, including both Gram-positive and Gram-negative coverage. Such antibiotics include carbapenems (e.gs. ertapenem, meropenem), piperacillin/tazobactam, third or/and fourth generation cephalosporins (e.g., ceftriaxone), and any combination of antibiotics that include both Gram-positive and Gram-negative coverage.

Table IV. Duration of antibiotics in practice of prophylactic antibiotics systematically given to patients with open fractures of extremities

	Injury severity not specified or for all levels		Gustilo type 1 and 2		Gustilo type 2 and 3		Gustilo type 3		Upper extremity†		Lower extremity§		Soil, marine or severely contaminated wounds		Gun low-velocity		Gun high-velocity	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Duration of antibiotics in practice																		
Up to 1 day	1	8.3	3	17.6					2	40.0	4	10.5						
2 to 3 days	1	8.3	5	29.4	1	50.0	4	20.0			8	21.1					1	33.3
4 to 7 days	1	8.3	3	17.6			2	10.0			7	18.4	1	50.0				
More than 7 days							2	10.0			5	13.2						
Duration not specified	9	75.0	6	35.3	1	50.0	12	60.0	3	60.0	14	36.8	1	50.0	1	100	2	66.7
Total	12	100	17	100	2	100	20	100	5	100	38	100	2	100	1	100	3	100

Table V. Regimen in recommendations of prophylactic antibiotics systematically given to patients with open fractures of extremities*

	Injury severity not specified or for all injuries		Gustilo type 1 and 2		Gustilo type 2 and 3		Gustilo type 3		Upper extremity†		Lower extremity§		Soil, marine or severely contaminated wounds		Gun velocity not specified		Gun low-velocity		Gun high-velocity	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Recommended drugs¶																				
Gram-positive coverage**	13	18.1	34	68.0							9	26.5	9	22.0	1	50.0	3	50.0	6	42.9
Gram-positive + anaerobic coverage††			2	4.0															1	7.1
Gram-positive + MRSA coverage§§	1	1.4											1	2.4						
Gram-negative coverage¶¶	1	1.4	2	4.0			5	10.9			1	2.9								
Broad coverage***	14	19.4	10	20.0	6	85.7	35	76.1			9	26.5	26	63.4	1	50.0	1	16.7	5	35.7
Broad + anaerobic coverage	3	4.2	1	2.0	1	14.3	3	6.5			1	2.9	4	9.8					1	7.1
Broad + MRSA coverage							1	2.2					1	2.4						
Broad + MRSA + anaerobic coverage	5	6.9									3	8.8								
Drug name not specified	35	48.6	1	2.0			2	4.3	4	100	11	32.4					2	33.3	1	7.1
Total	72	100	50	100	7	100	46	100	4	100	34	100	41	100	2	100	6	100	14	100

MRSA, methicillin-resistant *Staphylococcus aureus*

Notes:

* "Recommendation" was abstracted from review articles, surveys of surgeons, guidelines, textbooks and some clinical studies if they made recommendations.

† Upper extremity fractures include open fractures of radius, humerus and ulna, for all Gustilo types of injury severity.

§ Lower extremity fractures include open fractures of tibia, femur, knee, foot and ankle, forefoot, phalanx and calcaneus, for all Gustilo types of injury severity.

¶ Several authors of original sources recommended clindamycin as an alternative to beta-lactams in patients who are allergic to beta-lactams or in patients with suspected Group A Streptococcus infections.

** Gram-positive coverage includes first and second generation cephalosporins (e.g., cefazolin, cephalexin, cefamandole, cefuroxime and cephradine), cloxacillin or flucloxacillin or dicloxacillin, erythromycin, ampicillin or augmentin, amoxicillin or co-amoxiclav, penicillin, high-dose penicillin, penicillin G (benzyllpenicillin) and any combination of these drugs.

†† Anaerobic coverage includes metronidazole, clindamycin, beta-lactam/beta-lactamase inhibitors (e.g., ampicillin/sulbactam, piperacillin/tazobactam), and carbapenems.

§§ MRSA coverage includes vancomycin or teicoplanin.

¶¶ Gram-negative coverage, in this case, refers to aminoglycosides (e.g., gentamicin, tobramycin and amikacin).

*** "Broad" means broad-spectrum antibiotic coverage, including both Gram-positive and Gram-negative coverage. Such antibiotics include carbapenems (e.g., ertapenem, meropenem), meronem, piperacillin/tazobactam, third or/and fourth generation cephalosporins (e.g., ceftazidime, ceftriaxone and cefotaxime), and any combination of antibiotics that include both Gram-positive and Gram-negative coverage.

Table VI. Duration of antibiotics in recommendations of prophylactic antibiotics systematically given to patients with open fractures of extremities

	Injury severity not specified or for all injuries		Gustilo type 1 and 2		Gustilo type 2 and 3		Gustilo type 3		Upper extremity†		Lower extremity§		Soil, manure or severely contaminated wounds		Gun velocity not specified		Gun low-velocity		Gun high-velocity	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Recommended duration of antibiotic administration																				
Up to 1 day	14	19.4	17	34	1	14.3			1	25	4	11.8			1	50	1	16.7		
2 to 3 days	5	6.9	17	34	2	28.6	17	37			13	38.2	6	14.6	1	50	2	33.3	9	64.3
4 to 7 days	3	4.2					10	21.7			1	2.9	4	9.8						
More than 7 days							1	2.2	1	25	3	8.8								
Duration not specified	50	69.4	16	32	4	57.1	18	39.1	2	50	13	38.2	31	75.6			3	50	5	35.7
Total	72	100	50	100	7	100	46	100	4	100	34	100	41	100	2	100	6	100	14	100

Appendix 1. MEDLINE title and abstract search strategy for effects of antibiotic prophylaxis in patients with open fracture

1. antibiotics.mp. or exp Anti-Bacterial Agents/

2. antibiotic prophylaxis.mp. or exp Antibiotic Prophylaxis/

3. (anti-microb* or anti bact* or antibact*).mp.

4. (antibiotic* or antimicrob*).mp.

5. cephalothin.mp.

6. antibioprophylaxis.mp.

7. cloxacillin.mp.

8. exp AMOXICILLIN/ or AMOXICILLIN.mp.

9. exp Ampicillin/ or AMPICILLIN.mp.

10. CLAVULANIC ACID.mp.

11. AMOXICLAV.mp.

12. AUGMENTIN.mp.

13. TICARCILLIN.mp.

14. exp Cephalosporins/ or CEPHALOSPORIN*.mp.

15. (KEFLEX or CEFAMANDOLE or KEFADOL or CEFAZOLIN* or KEFZOL or CEFIXIME or SUPRAX).mp.

16. (CEFOTAXIME or CLAFORAN or CEFOXITIN or MEFOXIN or CEFPIROME or CEFROM or CEFPODOXIME).mp.

17. (ORELOX or CEFPROZIL or CEFZIL or CEFRADINE or VELOSEL or CEFTAZIDIM or ORTUM or KEFADIM).mp.

18. (CEFTRIAXONE or ROCEPHIN or CEFUROXIME or ZINACEF or ZINNAT or CEFONICID or AZTREONAM).mp.

19. (AZACTAM or IMIPENEM or ILASTATIN or PRIMAXIN or MEROPENEM).mp.

20. (TETRACYCLINE* or DETECLO or DEMECLEOCYCLIN or LEDERMYCIN or DOXYCYCLINE or VIBRAMYCIN).mp.

21. (MINOCYCLINE or MINOCINE or OXYTETRACYCLINE or TERRAMYCIN or MACROLIDE*).mp.

22. (ERYTHROMYCIN or ERYMAX or ERYTHROCIN or ERYTHROPED or AZITHROMYCIN or ZITHROMAX).mp.

23. (CLARITHROMYCIN or KLARICID or TELITHROMYCIN or KETEK or TRIMOXAZOLE or SEPTRIN).mp.

24. (TRIMETHOPRIM or MONOTRIM or TRIMOPAN or METRONIDAZOLE or FLAGYL or METROLYL).mp.

25. (PHENOXYMETHYLPENICILLIN or SULFAMETHOXAZOLE or OXACILLIN or CEPHALOTHIN or SULBACTAM).mp.

26. (OFLOXACIN or CLINDAMYCIN or GENTAMYCIN or VANCOMYCIN).mp.

27. (CEFACLOR or DISTACLOR or CEFADROXIL or BAXAN or CEFALEXIN or CEPOREX).mp.

28. (TIMENTIN or FLUCLOXACILLIN or FLUAMPICIL or MAGNAPEN or PIPERACILLIN or TAZOCIN).mp.

29. (streptomycin or cefalotin or dicloxacillin).mp.

30. or/1-29

31. exp fractures, open/

32. (orthopedic adj2 surg*).mp.

33. (open adj9 fracture*).mp.

34. ((open adj2 reduction) and fracture*).mp.

35. (Gustilo or Gustillo).mp.

36. anderson type*.mp.

37. (compound adj9 fracture*).mp.

38. ununited fractures.mp. or exp Fractures, Ununited/

39. fracture fixation.mp. or exp Fracture Fixation/

40. fracture*.mp. or exp Fractures, Bone/

41. (infect$ adj3 (bone$ or fracture$)).mp.

42. ((nonunion or non union) adj9 fracture*).tw.

43. or/31-42

44. 30 and 43

45. animals/ not humans/

46. 44 not 45

Appendix 2. Regimen in practice of prophylactic antibiotics systematically given to patients with open fractures of lower extremities by injury severity (published between January 2007 and June 2017)[*†]

	Lower extremity injury severity not specified or for all levels		Lower extremity Gustilo type 1 and 2		Lower extremity Gustilo type 2 and 3		Lower extremity Gustilo type 3	
	n	(%)	n	(%)	n	(%)	n	(%)
Antibiotic regimen in practice[§]								
Gram-positive coverage[¶]	3	17.6	3	42.9			1	7.7
Gram-negative[**] + anaerobic coverage[††]							1	7.7
Broad coverage[§§]	2	11.8	4	57.1			6	46.2
Broad + anaerobic coverage	1	5.9					1	7.7
Broad + MRSA[¶¶] + anaerobic coverage	1	5.9					1	7.7
Drug name not specified	10	58.8			1	100	3	23.1
Total	17	100	7	100	1	100	13	100

MRSA, methicillin-resistant *Staphylococcus aureus*

Notes:

* "Practice" was abstracted from multi-center or single-center randomized controlled trials (RCTs), cohort studies, case-control studies, single arm studies (including case series) and surveys of surgeons that indicate use of antibiotic prophylaxis among open fracture patients.

† Lower extremity fractures include open fractures of tibia, femur, ankle and calcaneus.

§ Clindamycin was used in patients with beta-lactam/penicillin allergies.

¶ Gram-positive coverage includes first and second generation cephalosporins (e.g., cefazolin, cephalexin, cefacidal, cefadroxil and cefuroxime), macrolide, ampicillin or augmentin, amoxicillin or co-amoxiclav, penicillin and any combination of these drugs.

** Gram-negative coverage, in this case, refers to aminoglycosides (e.g., gentamicin, tobramycin and amikacin).

†† Anaerobic coverage includes metronidazole (flagyl), clindamycin, beta-lactam/beta-lactamase inhibitors (e.g., ampicillin/sulbactam, piperacillin/tazobactam), and carbapenems.

§§ "Broad" means broad-spectrum antibiotic coverage, including both Gram-positive and Gram-negative coverage. Such antibiotics include carbapenems (e.gs. ertapenem, meropenem), piperacillin/tazobactam, third or/and fourth generation cephalosporins (e.g., ceftriaxone), and any combination of antibiotics that include both Gram-positive and Gram-negative coverage.

¶¶ MRSA coverage includes vancomycin or teicoplanin.

Appendix 3. Level of recommendations about prophylactic systemic antibiotic therapy for patients with open fractures of extremities (published between January 2007 and June 2017)

	Total		Injury severity not specified or for all injuries		Gustilo type 1 and 2		Gustilo type 2 and 3		Gustilo type 3		Upper extremity†		Lower extremity§		Soil, marine or severely contaminated wounds		Gun velocity not specified		Gun low-velocity		Gun high-velocity	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Recommendations: level of recommendations about whether antibiotics should to be systematically given to patients with open fractures of extremities, per article/book chapter/guideline																						
Must	252	91.3	58	80.6	47	94.0	7	100	43	93.5	3	75.0	33	97.1	41	100	2	100	4	66.7	14	100
Probably should	14	5.1	7	9.7	3	6.0			3	6.5									1	16.7		
Possibly should	2	0.7	1	1.4							1	25.0										
Uncertain	1	0.4																	1	16.7		
Probably should not	3	1.1	2	2.8									1	2.9								
Certainly should not	2*	0.7	2*	2.8																		
No opinion	2	0.7	2	2.8																		
Total	276	100	72	100	50	100	7	100	46	100	4	100	34	100	41	100	2	100	6	100	14	100

Note:

* Two review articles with recommendation of certainly should not use antibiotics only refer to fluoroquinolone.

Appendix 4. Regimen in recommendations of prophylactic antibiotics systematically given to patients with open fractures of lower extremities by injury severity (published between January 2007 and June 2017)*†

	Lower extremity injury severity not specified or for all levels		Lower extremity Gustilo type 1 and 2		Lower extremity Gustilo type 3	
	n	(%)	n	(%)	n	(%)
Recommended drugs§						
Gram-positive coverage¶	6	25.0	3	60.0		
Gram-negative coverage**					1	20.0
Broad coverage††	3	12.5	2	40.0	4	80.0
Broad + anaerobic coverage§§	1	4.2				
Broad + MRSA¶¶ + anaerobic coverage	3	12.5				
Drug name not specified	11	45.8				
Total	24	100	5	100	5	100

MRSA, methicillin-resistant *Staphylococcus aureus*

Notes:

* "Practice" was abstracted from multi-center or single-center randomized controlled trials (RCTs), cohort studies, case-control studies, single arm studies (including case series) and surveys of surgeons that indicate use of antibiotic prophylaxis among open fracture patients.

† Lower extremity fractures include open fractures of tibia, femur, knee, foot and ankle, forefoot, phalanx and calcaneus.

§ Clindamycin was used in patients with beta-lactam/penicillin allergies.

¶ Gram-positive coverage includes first and second generation cephalosporins (e.g., cefazolin, cephalexin, cefacidal, cefadroxil and cefuroxime), macrolide, ampicillin or augmentin, amoxicillin or co-amoxiclav, penicillin and any combination of these drugs.

** Gram-negative coverage, in this case, refers to aminoglycosides (e.g., gentamicin, tobramycin and amikacin).

†† "Broad" means broad-spectrum antibiotic coverage, including both Gram-positive and Gram-negative coverage. Such antibiotics include carbapenems (e.gs. ertapenem, meropenem), piperacillin/tazobactam, third or/and fourth generation cephalosporins (e.g., ceftriaxone), and any combination of antibiotics that include both Gram-positive and Gram-negative coverage.

§§ Anaerobic coverage includes metronidazole (flagyl), clindamycin, beta-lactam/beta-lactamase inhibitors (e.g., ampicillin/sulbactam, piperacillin/tazobactam), and carbapenems.

¶¶ MRSA coverage includes vancomycin or teicoplanin.

CHAPTER 4

Risk Factors for Persistent Post-surgical Pain after Tibia Fracture:

A Longitudinal Study

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Risk factors for persistent post-surgical pain after tibia fracture: a longitudinal study

Yaping Chang, MSc[1], Jason W. Busse, DC, PhD[1,2,3], Mohit Bhandari, PhD, MD[1,4], Wei Qi[5], Li Wang, PhD[2,3], Diane Heels-Ansdell, MSc[1], Qi Zhou, PhD[1], Lehana Thabane, PhD[1,6], Mei Wang, MSc[1],Kan Lun Zhu[7], Brad Petrisor, MD[4], Lin Jin, MD[1], Sean Alexander Kennedy, MD[8], Sheila Sprague, PhD[1,4], Paula McKay, BSc[4], Nicole Simunovic, MSc[4], Shiyun Hu, PhD, MD[9], Yuan Zhang, PhD[1], Ying Zhang, PhD[10], Gordon H Guyatt, MD, MSc[1] on behalf of the TRUST Investigators*

Affiliations and Correspondence

1. Department of Health Research Methods, Evidence, and Impact, McMaster University, 1280 Main Street West, Hamilton, Ontario, L8S 4K1, Canada

2. Department of Anesthesia, McMaster University, 1280 Main Street West, Hamilton, Ontario, L8S 4K1, Canada

3. Michael G. DeGroote Institute for Pain Research and Care, McMaster University, 1280 Main Street West, Hamilton, Ontario, L8S 4K1, Canada

4. Division of Orthopaedic Surgery, Department of Surgery, McMaster University, 1280 Main Street West, Hamilton, Ontario, L8S 4K1, Canada

5. Tianjin Centres for Disease Control and Prevention, 6 Huayuedao Road, Tianjin, 300041, China

6. Department of Medicine, McMaster University, 1280 Main Street West, Hamilton, Ontario, L8S 4K1, Canada

7. Department of Diagnostic Radiology, University of Toronto, 263 McCaul Street, Toronto, Ontario, M5T 1W7, Canada

8. Cardiovascular and Cerebrovascular Disease Prevention and Control Research Center of Zhejiang Province, Zhejiang Hospital, 12 Lingyin Road, Hangzhou, Zhejiang, 310013, China

9. Centre for Evaluation of Medicines, St. Joseph's Healthcare Hamilton, McMaster University, 25 Main Street West, Hamilton, Ontario, L8P 1H1, Canada

10. Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, 11 Bei San Huan Dong Lu, Beijing, 100029, China

*Please refer to Appendix 1 for a listing of the TRUST Investigators

ABSTRACT

Background: Although persistent post-surgical pain after tibia fracture is common, its predictors have received limited study.

Objectives: We used data collected as part of the Trial to Re-evaluate Ultrasound in the Treatment of Tibial Fractures (TRUST) to address, among patients with a tibial shaft fracture, the association between baseline characteristics and persistent pain up to 12 months post-operatively.

Methods: We defined our study outcome, the resolution of troublesome pain, as no more than mild persistent pain (pain score ≤3 on a 0-10 Numeric Rating Scale) at two consecutive follow-up visits. We used a multivariable Cox proportional hazards regression model for analysis.

Results: We included 481 patients with open or closed fractures of the tibia who underwent surgical repair. During the 12-month follow-up period, 313 of 481 (65.1%) participants reported resolution of pain. We found significant independent associations between resolution of pain and male sex (hazard ratio [HR]=1.34 [95% confidence interval (CI), 1.04 to 1.72]), non-smoking (HR=1.74 [95% CI, 1.33 to 2.29]) and alcohol consumption (HR=1.35 [95% CI, 1.06 to 1.73]). Age, obesity, type of fracture (closed versus open), additional injuries, and post-operative weight-bearing status did not predict resolution of pain.

Conclusions: In our study, non-medical factors were predictive of persistent post-surgical pain after tibial fracture repair, whereas injury severity was not. Results of the study will alert clinicians of the higher risk of persistent

post-operative pain in female smokers who do not use alcohol, and allow them to use this information as a means to counsel female smokers to discontinue smoking. Further prospective studies are needed to confirm or refute the findings in our study.

Key words: persistent pain; post-surgery; tibial shaft fracture; predictor

1. Introduction

Tibia fractures are the most frequent type of long bone fracture [1-3]. The National Center for Health Statistics reported 492,000 tibia fractures per year in the United States [3]. Tibia fractures often require prolonged rehabilitation or multiple operative procedures to achieve maximal functional recovery.

Persistent post-surgical pain (PPSP), defined in the 11th version of the International Classification of Diseases of the World Health Organization (WHO) as pain that lasts for at least three months after a surgical procedure excluding other causes of pain [4-6], is common amongst patients who undergo surgery following lower extremity fractures [7]. Greater duration and severity of post-surgical pain is associated with less mobility [8], restrictions in activities of daily living, and reduced quality of life [2,3,9-11].

Although PPSP after fracture repair is common, predictors of persistent pain have received limited study. Therefore, to determine the association between patients' characteristics and PPSP in adults with tibial fracture, we assessed the association between pain status at the time of surgery and PPSP up to 12 months postoperatively.

2. Methods

2.1 Study Design and Participants

The current study used data collected as part of a large, prospective, multi-center randomized controlled trial, the Trial to Re-evaluate Ultrasound in the Treatment of Tibial Fractures (TRUST) [12,13]. The TRUST Investigators (Appendix 1) evaluated the impact of low-intensity, pulsed ultrasound applied to tibial shaft fractures treated with intramedullary nailing on functional status, time to radiographic healing of fractures and rates of nonunion. The trial enrolled adults aged 18 years or older, with an open or closed tibial fracture amenable to intramedullary nail fixation seen at 43 participating centers across Canada and the United States between October 2008 and September 2012 (last assessment April 2013, data of last contact in May 2013). The trial found no benefit of the Sonic Accelerated Fracture Healing System (SAFHS®) device applied within 14 days of fracture nailing treatment versus placebo [12,13].

The McMaster University Research Ethics Board and local ethics boards at each participating site approved the TRUST protocol (REB #08-171). All participants provided written informed consent prior to participation. The TRUST pilot study [12] and the TRUST definitive trial [13] have been published elsewhere.

2.2 Measurement of PPSP

Patients were evaluated prior to surgery and at 6, 12, 18, 26, 32, 38, 44 and 52 weeks after surgical repair of their tibia fractures. At each of these visits, patients rated their level of pain intensity on a 0-10 Numeric Rating Scale, with 0

representing no pain and 10 representing the worst pain possible.

2.3 Definition of outcome - Resolution of troublesome pain

In the current study, we defined PPSP as pain persisting either continuously or intermittently for 3 months or more after surgery [4-6]. We defined our study outcome, the resolution of troublesome pain, as a patient report of mild or no pain (pain score ≤3) [14,15] at two consecutive follow-up visits, and pain score would not increase beyond 3 anymore.

2.4 Independent Variables

We present continuous variables as means and standard deviations and categorical and binary variables as proportions. Orthopedic surgeons and pain researchers (MB, JWB, BP and GG) identified the following possible predictors of post-operative pain: age, sex, body mass index (BMI), smoking status, alcohol use, diabetes, kidney disease or renal insufficiency, vascular disease, rheumatoid arthritis, co-morbidity requiring chronic steroid use, fracture type (open from Gustilo type I-IIIB or closed from Tscherne grade 0-3), whether there were additional injuries, intramedullary nailing with or without reaming, and post-operative weight-bearing status on the day of surgery (non, partial or full).

Based on the standard BMI cutoff points that the WHO has recommended for classification of obesity (≥30 kg/m^2) [16], we categorized BMI into two groups: 1) non-obese (BMI <30 kg/m^2) and 2) obese (BMI ≥30 kg/m^2). We also categorized post-operative weight-bearing status into two groups: 1) non weight-bearing and 2)

partial or full weight-bearing.

2.5 Statistical Analysis

Before entering the potential prognostic factors into the multivariable models, we examined all pair-wise correlations by calculating the *r* index, considering the threshold of highly correlated to be > 0.7 [17]. For binary and categorical variables we looked at Phi or Cramer's V statistics; for continuous variables we looked at Pearson's correlation coefficient; and for continuous and categorical variables we looked at Point-Biserial correlation or the correlation coefficient from the R-square from of the ANOVA analysis [17]. For variables with correlations over 0.7, we planned to include only the variables that we considered most likely to be predictive of PPSP. We used variance inflation factor (VIF) to detect the multicollinearity of variables and planned to exclude the variables with VIF over 4.0 [18]. We also excluded variables in which there were less than 10 events in each of the groups with or without the presence of the putative predictor [19]. To determine the 12-month association between possible predictors and resolution of troublesome pain, we conducted a time-to-event analysis by including all other pre-specified variables in a multivariable Cox proportional hazards regression model [20] and tested the model to ensure the proportional hazard assumption was met. We consulted the orthopedic surgeon (BP) for any postulated interactions prior to analysis.

We report the number of participants and proportions at their last follow-ups. We look at the distribution of duration of follow-up in those who had PPSP. We

report all association estimates as hazard ratios (HRs) and 95% confidence intervals (CIs). All calculated P-values are two-tailed, with the criterion for statistical significance set at 0.05. We calculated the pair-wise correlations for variables using SAS version 9.4 (SAS Institute Inc., NC, USA) and performed the remaining analyses using SPSS version 24.0 (IBM Corp., NY, USA).

3. Results

Of 501 patients enrolled in the TRUST study, two did not have any records of pain measurement, and 18 had only a baseline record of pain measurement. The remaining 481 patients, all of whom had data available for pain scores at least three months after surgery, were included in the analysis. Table I summarizes the characteristics of these 481 patients. No participants had kidney disease or renal insufficiency, vascular disease or rheumatoid arthritis. There were fewer than 10 events in each of the groups of diabetes, a comorbidity requiring chronic steroid use and type of fixation (Table I). We therefore did not consider any of these potential predictors of troublesome post-operative pain further.

We were able to follow the majority of patients (301/481, 62.6%) for the full 12 months post-surgery. Of the 481 participants, 313 (65.1%) experienced resolution of troublesome pain over 12 months. Resolution of pain was related to duration of follow-up. The greatest reduction in the proportion experiencing important PPSP occurred between 18 and 26 weeks of follow-up. For those followed for 26 weeks or more, there was little difference in the proportion with persistent troublesome pain (Table II, Figure 1). If one considers only those followed for 26 weeks or more, 297/402 patients (73.9%) achieved resolution of PPSP. No two variables were correlated with one another at the threshold value of 0.7 or higher (Appendix 2). No variables had VIF at the threshold value of 4.0 or higher (Appendix 3).

In the multivariable Cox survival regression, we found significant independent associations between resolution of troublesome pain and male sex

(HR=1.34, 95% CI 1.04 to 1.72; p value=0.02), non-smoking (HR=1.74, 95% CI, 1.33 to 2.29; p value < 0.001) and alcohol consumption (HR=1.35, 95% CI, 1.06 to 1.73; p value=0.02). We did not find significant associations between PPSP and age, obesity, type of fracture (closed versus open), additional injuries or post-operative weight-bearing status (Table III, Figure 2). In every case, we found no violation of the proportional hazards assumption (Appendix 4). The surgeon did not have concerns about any postulated interactions.

4. Discussion

We found that 65.1% of patients who underwent repair of closed or open tibial shaft fracture achieved stable resolution of troublesome pain 3 to 12 months after surgery; the remaining 34.9% continued to report PPSP. Few patients achieved resolution prior to 26 weeks; of those followed for 36 weeks or more almost three quarters of patients achieved resolution (Table II). Independent predictors of resolution of troublesome pain were male sex, non-smoking and drinking alcohol (Table III). The association was particularly strong for smoking status: non-smokers were almost twice likely to be free of pain than were smokers (HR=1.74, 95% CI, 1.33 to 2.29). We did not find significant association between age, obesity, additional injuries, post-operative weight-bearing status on the day of surgery and, perhaps most surprisingly, type of fracture (open versus closed) and PPSP.

Strengths of this study include multicenter participation from two countries, which enhanced generalizability, a sample size sufficient to generate satisfactory confidence intervals, a follow-up period of one-year achieved in the majority of patients, a patient-important and conservative outcome definition of resolution of troublesome pain, [12,13] and analytic approaches.

However, this study also has limitations. First, the study failed to obtain 100% follow-up for all enrolled patients. We applied a time-to-event analysis (Cox regression) and provided results of complete observed data, which provides some assurances that loss to follow-up was unlikely to bias our results. Second, according to design of the TRUST, we were only able to measure our event,

resolution of pain, at time of patient visits (6, 12, 18, 26, 32, 38, 44 and 52 weeks after surgery), rather than the actual time point of the pain resolution. Finally, data regarding a number of other potential predictors that other investigators have addressed was not available in our cohort. In particular, we did not explore the role of level of education [21-25], pre- or post-injury depression, anxiety and/or distress [21-23,26-28], acute post-surgical pain [21-23,25], pre-surgical physical dysfunction [21,23,25], somatic pre-occupation or impaired coping [29-32], receipt of disability benefits/involvement in litigation [33], or use of opioids [26,34,35], which may be relevant in terms of prognostic implications.

PPSP is common among patients with orthopedic injuries. Rivara and colleagues reported that in 527 patients with lower extremity fractures, 63.9% reported some pain at one year after injury with a mean (SD) severity of pain of 5.6 (4.9) on a 0 (none) to 10 (worst possible pain) point scale [21]. Castillo and colleagues reported that 33.3% had moderate or severe pain intensity among patients with tibia fractures at 7 years after injury [26]. The proportion of PPSP in our study, approximately 35% for all follow-up and just over 25% for those followed six months or more, was substantially lower than the value reported by Rivara, though not substantially different than Castillo [21,26]. Rivara did not separate the results of patients with tibia fractures from the overall results, which included patients with any type of lower extremity fracture [21]. Also, Rivara only reported the proportion of any pain [21] while Castilo reported proportions of no pain, low, moderate and severe pain separately [26]. These may explain the difference.

The association we found of female sex being at a higher risk of PPSP is consistent with the results of prior studies examining trauma patients [21-23,36]. A large, prospective observational study by Holbrook and colleagues indicated that women had not only worse pain, but also significantly worse short- and long-term functional and psychological outcomes after major trauma than men [37]. The mechanisms of gender differences observed in chronic pain are not yet clear. Hypothetical explanations may include generic [38], socio-psychological [37,39], and enhanced central sensitization in women after orthopedic trauma [40].

Our finding of the association between smoking and persistence of troublesome pain is also consistent with prior studies [21-23,41]. For instance, Rivara and colleagues found that pre-injury smokers had higher risk of pain presence and pain severity one year after trauma: mean (SD) scores of pain were 5.8 (4.9) for smokers and 5.2 (4.6) for non-smokers, respectively ($p<0.001$) [21].

With regard to alcohol assumption and PPSP, prior studies have reported inconsistent results [22,23]. Castillo and colleagues found high levels of average alcohol consumption at baseline predicted chronic pain 7 years after limb threatening lower extremity trauma [26]. In a study by Rivara and colleagues, self-reported hazardous alcohol drinkers had lower pain severity, but did not differ in pain presence compared to the other two groups of nonhazardous drinkers or non-drinkers one year after trauma [21]. Thus, our finding of alcohol consumption being associated with a lower risk of PPSP is consistent with the reports by Walker-Bone and Rivara [21,36] but not with the report by Castillo [26]. The data in our study did not allow us to distinguish between hazardous and nonhazardous

drinkers.

We did not find obesity and severity of injury to be predictors of PPSP. Our results are consistent with a Dutch cohort study of trauma patients in terms of BMI [24] and a systematic review of orthopedic trauma patients in terms of injury severity [22]. Prior evidence also indicated that older age is associated with persistent pain after trauma surgery [22,23]; however, age was not associated with PPSP in our cohort.

Our findings suggest that clinicians should be particularly alert to the possibility of troublesome post-operative pain in female smokers who do not drink alcohol. Clinicians may consider counseling patients to discontinue smoking, inform them that they are at nearly double the risk of incidence of troublesome post-operative pain (in addition to the long-term adverse health consequences of smoking). Our findings regarding associations of post-operative pain with female sex and smoking appear robust: they are consistent with a number of prior reports. Subsequent prospective studies addressing issues of age and alcohol consumption would likely add further valuable evidence. Such studies would ideally have a sufficient sample size, follow-up duration, completeness of follow-up, and collect data on all possible predictors of PPSP.

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CONFLICT OF INTEREST

No conflicts declared.

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Table I. Baseline characteristics of study participants

	Total	Resolution of troublesome pain	PPSP*
	N (% in column)	N (% in row)	N (% in row)
Total	481 (100)	313 (65.1)	168 (34.9)
Age (years)	37.9 (14.0) †	38.7 (14.5) †	36.3 (12.8) †
Sex			
Male	331 (68.8)	217 (65.6)	114 (34.4)
Female	150 (31.2)	96 (64.0)	54 (36.0)
BMI§			
<30	349 (73.5)	222 (63.6)	127 (36.4)
≥30	126 (26.5)	85 (67.5)	41 (32.5)
Smoking			
No	330 (68.6)	236 (71.5)	94 (28.5)
Yes	151 (31.4)	77 (51.0)	74 (49.0)
Alcohol consumption			
Yes	317 (65.9)	210 (66.2)	107 (33.8)
No	164 (34.1)	103 (62.8)	61 (37.2)
Diabetes¶			
No	453 (94.4)	294 (64.9)	159 (35.1)
Yes	27 (5.6)	18 (66.7)	9 (33.3)
Comorbidity requiring chronic steroid use**			
No	471 (98.1)	306 (65.0)	165 (35.0)
Yes	9 (1.9)	6 (66.7)	3 (33.3)
Type of fracture			
Closed	371 (77.1)	252 (67.9)	119 (32.1)
Open	110 (22.9)	61 (55.5)	49 (44.5)
Additional injuries			
No	71 (14.8)	47 (66.2)	24 (33.8)
Yes	410 (85.2)	266 (64.9)	144 (35.1)
Type of fixation ††			
Nail with prior reaming	478 (99.6)	311 (65.1)	167 (34.9)
Nail without prior reaming	2 (0.4)	2 (100)	0 (0)
Post-operative weight-bearing status on the day of surgery			
Full or partial weight-bearing	264 (54.9)	174 (65.9)	90 (34.1)
Non-weight bearing	217 (45.1)	139 (64.1)	78 (35.9)

Notes:

* PPSP: persistent post-surgical pain

† Mean and standard deviation

§ n=475 (349 and 126); BMI: body mass index. BMI<30: overweight, normal weight and underweight; BMI≥30: obese

¶ n=480 (453 and 27)

** n=480 (471 and 9)

†† n=480 (478 and 2)

Table II. Distribution of duration of participants' follow-ups among patients with persistent post-surgical pain (≥12 weeks, absolute number of patients)

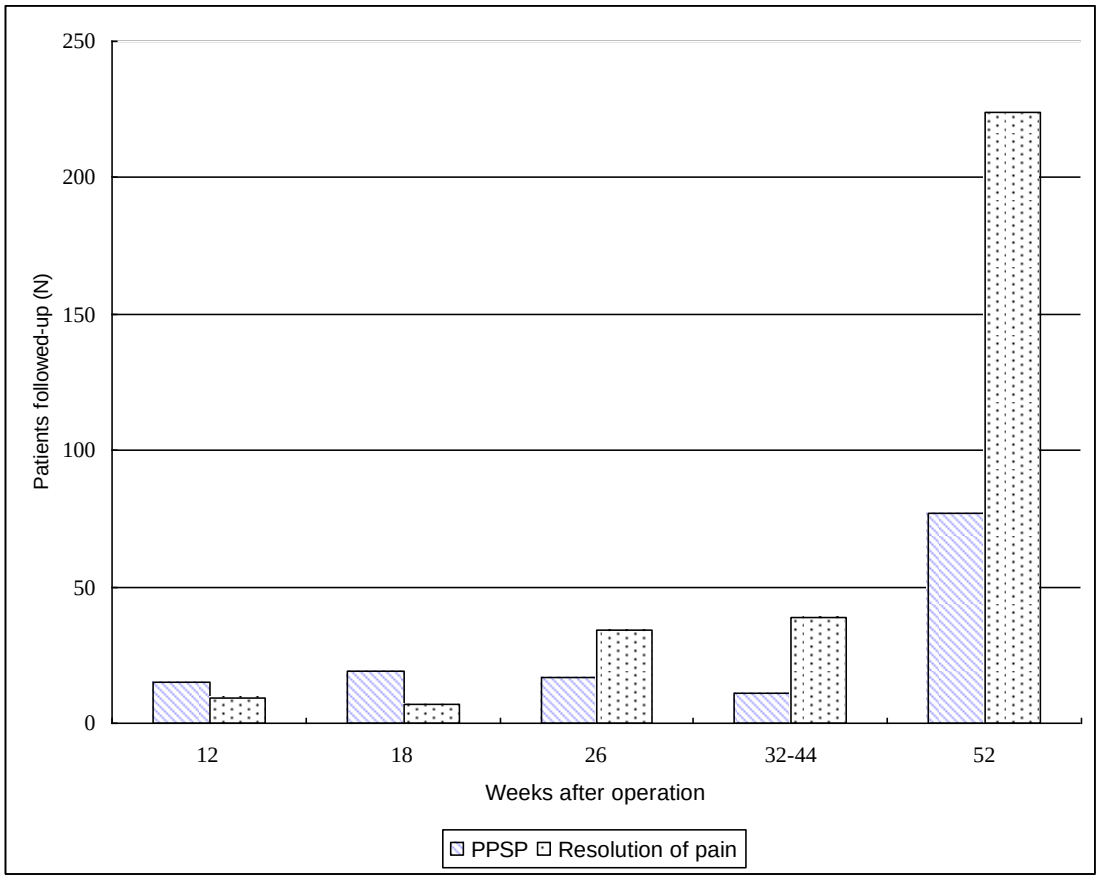
	Total	Patients with PPSP*	
	N	N	(%)
Total	452	139	
12 weeks	24	15	(62.5)
18 weeks	26	19	(73.1)
26 weeks	51	17	(33.3)
32, 38 and 44 weeks	50	11	(22.0)
52 weeks	301	77	(25.6)

Note:
* PPSP: persistent post-surgical pain

Table III. Predictors of resolution of post-surgical pain in study participants (Cox survival model, adjusted analysis)

	Hazard Ratio (95% Confidence Interval)	P value
Total		
Age, per 10 years	1.04 (0.96-1.13)	0.36
Sex		
Male	**1.34 (1.04-1.72)**	**0.02**
Female	1.00	
BMI*		
<30	1.03 (0.80-1.32)	0.83
≥30	1.00	
Smoking		
No	**1.74 (1.33-2.29)**	**<0.001**
Yes	1.00	
Alcohol consumption		
Yes	**1.35 (1.06-1.73)**	**0.02**
No	1.00	
Type of fracture		
Closed	1.12 (0.84-1.49)	0.45
Open	1.00	
Additional injuries		
No	0.90 (0.65-1.24)	0.50
Yes	1.00	
Post-operative weight-bearing status on the day of surgery		
Full or partial weight-bearing	1.12 (0.88-1.41)	0.36
Non-weight bearing	1.00	

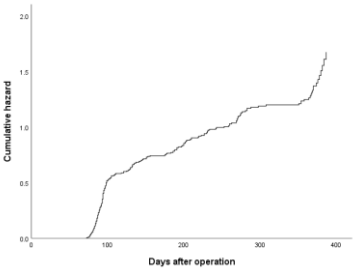
Note:
* BMI: body mass index



Note:
PPSP: persistent post-surgical pain

Fig. 1 Distribution of duration of participants' follow-ups (≥12 weeks, absolute number of patients)

a.



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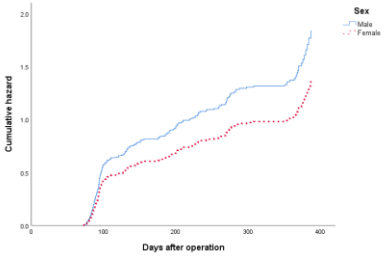

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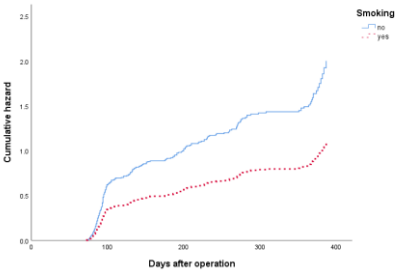


d.

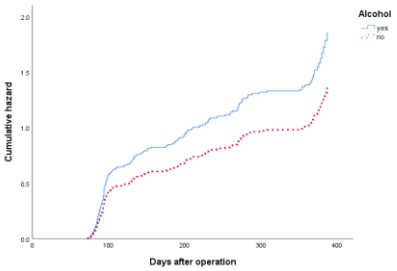


Fig. 2 Kaplan-Meier curves for resolution of troublesome post-operative pain amongst patients with tibial fracture: a. overall results; b. results by gender; c. results by smoking status; d. results by alcohol consumption status

Appendix 1: TRUST Investigators:

Steering Committee: Mohit Bhandari (Chair), Jason W. Busse, Thomas A. Einhorn, James D. Heckman, Kwok-Sui Leung, Emil H. Schemitsch, Paul Tornetta III, Stephen D. Walter, Gordon H. Guyatt; **Central Adjudication Committee:** Mohit Bhandari (Chair), Emil H. Schemitsch, David Sanders; **TRUST Methods Centre Staff: McMaster University, Hamilton, Ontario:** Sheila Sprague, Paula McKay, Kim Madden, Nicole Simunovic, Diane Heels-Ansdell, Lisa Buckingham, Helena Viveiros, Qi Zhou, Marilyn Swinton.; **TRUST Data Safety and Monitoring Board Members:** George A. Tomlinson (Chair), Mark Munro, Rob GHH Nelissen.

TRUST Study Investigators: Greenville Health System – Kyle J. Jeray, J. Scott Broderick, Stephanie L. Tanner, Becky Snider.

Orthopaedics of Indianapolis – Dean Maar, Renn Crichlow, Greg Reveal, David Kaehr, Joseph Baele, Kevin Douglas Scheid, David Brokaw, Tim Weber, Brad Jelen, Matt Edison, Anna Clark

Temple University Hospital – Saqib Rehman, Alyssa A. Schaffer, Asif M. Ilyas, J. Milo Sewards, Joanne M. Donnelly.

QEII Health Sciences Centre – Chad Coles, Michael Dunbar, David Alexander, David Amirault, Catherine Coady, Mark Glazebrook, Michael Gross, David Johnston, Ross Leighton, William Oxner, Gerald Reardon, William Stanish, Glen Richardson, Michael Biddulph, Kelly Trask, Gwen Dobbin, Shelley MacDonald.

Duke University Medical Center – Steven Olson, Robert Zura, Rachel Reilly,

Maria Manson.

University of California, San Francisco/San Francisco General Hospital – Theodore Miclau, Saam Morshed, Amir Matityahu, Utku Kandemir, Tigist Belaye, Jonathan Kwong.

Vancouver General Hospital – Peter O'Brien, Piotr Blachut, Pierre Guy, Henry Broekhuyse, Kelly A Lefaivre, Raman Johal, Irene Leung.

Orthopaedic Speciality Associates – Cory A. Collinge, Keith Watson, Derek Dombroski, Tara Craig.

West Virginia University – David Hubbard, Michelle A Bramer, John France, E. Barry McDonough, George K. Bal, John P. Lubicky, Brock Lindsey, Robert Santrock, Scott Daffner, Sheila Rye, Christina Carey, Stacy Skidmore, Nina Clovis.

Rothman Institute – Javad Parvizi, Matt Austin, John A. Abraham, Charlie Getz, James Purtill, Steven Raikin, Tiffany Morrison, Bora Og.

Emory University – Thomas Moore, George Wright, Allen McDonald, Maria Davila, Lauren Rabach, Whitney Barnes.

Cooper University Hospital – Kenneth Graf, Robert Ostrum, David Fuller, Robert Marburger

University of Missouri Health Care - Gregory J. Della Rocca, Brett D. Crist, Yvonne M. Murtha, David A. Volgas, James P. Stannard, Toni K. Kliewer, Sharon L. Jarrett, Kelly A. Moore, Kathleen Markley, Angela Ballew, Abigail K. Stidham.

Foothills Medical Centre – Paul Duffy, Robert Korley, Shannon Puloski, Richard Buckley, Kelly Johnston, Kimberly Carcary, Ross McKercher.

University of Kentucky – Jeffrey Selby, Mauro Giordani, Eric Moghadamian, Daniel D. Primm, Raymond D. Wright Jr, Brandon Bruce, Justin Perry, Amy Trivette, Regina Mosley, Melinda M. Dowden-Kruger, Dorothy Ross.

Insall Scott Kelly Institute – Craig S. Radnay, Timothy Reish, Michael Kang, William Long, Michael Nett, Priya Chadha, Elizabeth H. Jett, Jesie Paniagua.

Florida Orthopaedic Institute – H. Claude Sagi, Anthony Infante, David T. Watson, Daniel Chan, George Haidukewych, Anjan Shah, Barbara Steverson, Veronica Colon.

Eastern Maine Medical Center – David Carmack, Rajendra Tripathi, F. Parke Oldenburg, Denise Michaud, Teresa White.

University of South Alabama – Jorge Alonso, Kelley Prutzman.

University of British Columbia/Royal Columbian Hospital/Fraser Health Authority – Trevor Stone, Kelly Apostle, Dory Boyer, Farhad Moola, Bertrand Perey, Darius Viskontas, H. Michael Lemke, Robert McCormack, Mauri Zomar, Karyn Moon, Raely Moon, Amber Oatt.

Shrock Orthopaedic Research – Kevin Shrock, Matthew Wells, Natalie Shrock

Denver Health – David Hak, Philip F Stahel, Mark Hammerberg, Cyril Mauffrey, Corey Henderson,

Erin Ross, Douglas Gibula, Hannah Gissel.

University of Virginia – David B. Weiss, David Kahler, Jacquelyn Sedlock, Vasantha Reddi, Veronica C. Lester-Ballard, Wendy M. Novicoff.

Pensacola Research Consultants Inc – Eugene Jean Dabezies, Kurt Morrison, Kirby Turnage, Robert Lurate, Gay Crawley, Donna Lawson, Iris McCants, Anna

Brunson, Mary Whitaker, Stefanie White, Michael Ellis.

Sunnybrook Health Sciences Centre – Hans Kreder, Terry S. Axelrod, Joel A. Finkelstein, Patrick D.G. Henry, Richard Jenkinson, John J. Murnaghan, Diane Nam, Markku Nousiainen, Sebastian Rodriguez-Elizalde, Veronica M.R. Wadey, Robin Richards, David Stephen and Albert Yee, Katrine Milner, Monica Kunz, Melanie MacNevin, Ayushi Dhingra.

London Health Sciences Centre – Abdel-Rahman Lawendy, David Sanders, Christina Tieszer.

Texas Orthopedic Specialists – O. David Taunton Jr., Jason Ahuero, Amber Morgan.

University of Kansas Medical Center – Archie Heddings, John Sojka, Michael Tilley, Sharon Bradshaw.

Orthopaedic Associates of Michigan – Clifford B. Jones, James R. Ringler, Terrence J. Endres, Debra L. Sietsema, Jane E. Walker, Susan M. Engerman.

Lahey Hospital and Medical Center – Andrew Marcantonio, Michael S. Kain, John Garfi.

Texas Orthopedics, Sports & Rehabilitation Associates – Christopher M. Danney, Marc DeHart, Scott Smith, Barbara Bergin, Joel Hurt, Tyler Miller, Todd Curry, Karl Adcock.

Marshall University – Franklin D. Shuler, Amber Simmons.

Southlake Regional Health Centre – Christopher Lindsay, Cleo Rogakou, Pat Gamble, Debbie Nemtean.

KSF Orthopaedic Center– John P. Seaberg, Derrick Clay, Cameron Wood, Todd

Curry, Tyler Miller

Clinical Research Niagara, Inc. – David Martin, John Song, Robert Josefchak, Paul Robert, Avril McKenna-Norton, Marnie-Lynn Sennett, Olwen McKenna.

York Hospital/WellSpan Health – Thomas DiPasquale, Mark Richardson, Paul Muccino, Adrienne Brandon.

Mission Hospital – H. Michael Frisch, C. Michael LeCroy, Susan Sutherland, Rachel Alosky, Leslie Elliott, Lynne Hampton, Tracy Nanney, Claudine Cuento, Stephanie Shepard.

Louisiana State University – Melissa Gorman, Peter Krause, Ronald Rooney, Jennifer Perilloux.

Inova Fairfax Hospital – Robert A. Hymes, Cary Schwartzbach, A. Stephen Malekzadeh, Jeff E. Schulman, Daniel Dziadosz, Laura Thurston, Jihui Li.

Texas Sports Medicine Institute – Michael C. Maier, Tyler Miller, Todd Curry.

Anthony G. Sanzone, MD, Inc – Anthony Sanzone, Kaelin Schickedanz.

Orthopaedic Associates of South Broward, P.A – Steven D. Steinlauf, Richard E. Strain, Daniel Chan, Warren Grossman, Judy Magnum.

University Orthopaedics Center – Bradley A. Barter, Douglas Roeshot, Thomas Ellis, Edwin Rogusky, Paula Sensiba, Andrew Marcus, Kenneth Cherry, Sue Jepson, Jennifer Gramley.

Appendix 2 Correlation of factors considered in Cox survival model (*r*)

	Age	Sex	BMI	Smoking	Alcohol	Type of fracture	Additional injuries
Sex	-0.13						
BMI*	-0.08	0.07					
Smoking	0.17	-0.14	-0.08				
Alcohol	-0.12	0.10	0.09	-0.21			
Type of fracture	0.08	-0.11	-0.07	0.11	-0.04		
Additional injuries	-0.11	0.07	-0.02	0.04	0.003	0.05	
Post-operative weight-bearing status	-0.14	0.16	0.01	-0.08	0.04	-0.12	0.13

Note:
* BMI: body mass index

Appendix 3. Assessment of multicollinearity of variables

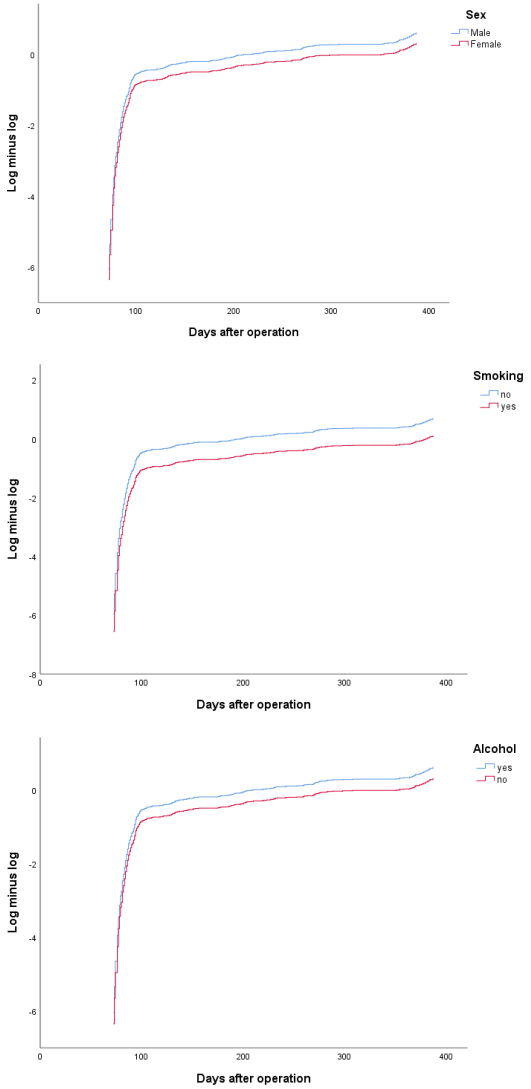
Variables	VIF*
Age	1.077
Sex	1.063
BMI†	1.023
Smoking	1.096
Alcohol	1.066
Type of fracture	1.041
Additional injuries	1.041
Post-operative weight-bearing status	1.065

Notes:
* VIF: variance inflation factor
† BMI: body mass index

Appendix 4. Assessment of proportional hazard assumption for variables in Cox survival model

Variables	P value
Age	0.834
Sex	0.270
BMI*	0.223
Smoking	0.393
Alcohol	0.124
Type of fracture	0.530
Additional injuries	0.239
Post-operative weight-bearing status	0.287

Note:
* BMI: body mass index



CHAPTER 5

Conclusion

The current thesis includes three individual studies with a focus on the prognosis and management of patients who have injuries necessitating orthopedic surgeries, in particular, fractures of extremities. We used different methods to collect and analyze the data. I list the key findings from the three studies below:

I. Effects of Antibiotic Prophylaxis in Patients with Open Fracture of the Extremities: A Systematic Review of Randomized Controlled Trials

i) There is moderate quality evidence that patients receiving, versus not receiving, antibiotic prophylaxis experience a large and important reduction in infection rate (risk ratio (RR) 0.37, 95% confidence interval (CI) 0.21-0.66, absolute risk reduction 9.6%, 95% CI 5.2% to 12.1%).

ii) We found no difference in infection rate with longer (3 to 5 days) versus shorter (1 day) duration of antibiotics (RR 0.97, 95% CI 0.69-1.37), but the evidence is only low quality.

iii) Results of RCTs performed to date provide evidence that antibiotic prophylaxis reduces subsequent infection, and that courses as short as one day are as effective as courses of 3 to 5 days, though evidence warrants only low to moderate confidence.

iv) Results of RCTs provide very limited guidance regarding the optimal

antibiotics to use in prophylaxis.

II. Antibiotic Prophylaxis in the Management of Open Fractures: A Systematic Survey of Current Practice and Recommendations

v) Clinicians and investigators' practices, as well as expert recommendations, over the last decade strongly support early systemic antibiotics prophylaxis for patients with open fractures of extremities. Differences in antibiotic regimens, doses and durations of administration remain in both practice and recommendations.

vi) In practice, a majority used systemic antibiotics with both gram-positive and gram-negative coverage, and continued the administration for 2 to 3 days.

vii) Most recommendations suggested gram-positive coverage for less severe injuries i.e., Gustilo type 1 and 2 open fractures, and administration duration of 3 days or less (half suggested 1 day).

viii) For more severe injuries, i.e., Gustilo type 3 open fractures, most recommendations suggested broad antimicrobial coverage continued for 2 to 3 days.

ix) The most important difference between recommendations and practice was that, when authors made recommendations for Gustilo 1 or 2 open fractures as a group, they recommended restricting antibiotic use to agents with exclusively gram-positive coverage, while in practice surgeons used broader coverage. When authors grouped Gustilo 2 and 3 fractures together, almost all suggested using broad coverage with

reliable activity against both gram-positive and gram-negative organisms.

III. Risk Factors for Persistent Post-surgical Pain after Tibia Fracture: A Longitudinal Study

x) 313 of 481 (65.1%) patients with open or closed fractures of the tibia reported resolution of pain after surgery.

xi) We found significant independent associations between resolution of pain and male sex (hazard ratio [HR]=1.34, 95% CI, 1.04 to 1.72), non-smoking (HR=1.74 [95% CI, 1.33 to 2.29]) and alcohol consumption (HR=1.35 [95% CI, 1.06 to 1.73]).

xii) Age, obesity, type of fracture (closed versus open), additional injuries, and post-operative weight-bearing status did not predict resolution of pain.

Weaknesses of the current thesis are primarily related to the limitation in evidence. RCTs comparing antibiotic prophylaxis versus no prophylaxis, and RCTs comparing different regimens, routes of administration, dose, and/or duration of antibiotic administration are very limited. The included RCTs have limitations of relatively small sample size and high risk of bias. This led to our low to moderate ratings of confidence in estimates of effectiveness of the intervention. Current recommendations, although they are many in numbers of publications, have a very limited evidence base supporting their advice regarding the choice of optimal regimens, dose and duration of antibiotic administration among patients with open

fractures of extremities depending on different injury severity.

Nevertheless, our survey of practice and recommendations represents a valuable contribution: the work represents the first systematic survey addressing both what studies report in terms of use of antibiotics in prophylaxis in open fractures, and what experts recommend. Many clinicians may, under circumstances of low quality evidence, find experts' views of the optimal approaches helpful.

With regard to Chapter 4, our longitudinal study using results from a randomized trial to explore predictors of post-operative pain, data proved unavailable for some variables that may be relevant in terms of PPSP prognostic implications, not all patients were followed for the full year, and pain ratings were not available for some follow-up visits in patients followed for longer durations.

In relation to our findings, researchers may consider future study directions listed below:

i) Given limited and low-quality evidence regarding optimal antibiotic prophylaxis for open fractures, a large, multi-center, low risk of bias RCT enrolling representative populations and addressing duration of antibiotics (1 day versus 3 or 5 days as prophylaxis) may be the next optimal step in investigation.

ii) For Gustilo type 2 open fractures, whether antibiotics with gram-positive has similar effectiveness with antibiotics with broad coverage. Researchers may consider sub-group participants' analysis in a large RCT, or design a

separate RCT to address the question.

iii) Our findings regarding associations of post-operative pain with female sex and smoking appear robust: they are consistent with a number of prior reports. Subsequent prospective studies addressing issues of age and alcohol consumption would likely add further valuable evidence. Such studies would ideally have a sufficient sample size, follow-up duration, completeness of follow-up, and collect data on all possible predictors of PPSP.