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Is There a Difference in Infection Risk Between Single and Multiple Doses of Prophylactic Antibiotics? A Meta-analysis

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Abstract

Background The prevention of surgical site infection guidelines issued by the Centers for Disease Control and Prevention (CDC) recently recommended that only a single dose of preoperative antibiotics be administered to patients undergoing clean-contaminated procedures based on data from a variety of surgical disciplines. For

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orthopaedic procedures, where postoperative infections can have significant consequences, the existing evidence for this recommendation is widely debated.

Questions/purposes Is there a difference in postoperative infection risk when utilizing a single dose of preoperative antibiotics compared with multiple doses of perioperative antibiotics for orthopaedic procedures where implants are placed?

Methods MEDLINE, EMBASE, Google Scholar, and Cochrane were systematically reviewed for randomized controlled trials (RCTs) of a single dose of preoperative antibiotics compared with pre- and postoperative prophylaxis from 1980 to 2017 for all orthopaedic procedures where implants were being placed. Infection (both superficial and deep) as a primary outcome through all available followup was required for inclusion. Fourteen RCTs detailing 9691 orthopaedic procedures were included for analysis, including seven arthroplasty, one spine, and six general orthopaedic trials (two specific to hip fracture fixation). Pooled infection outcomes were analyzed with random-effects modeling in light of study heterogeneity. Bias was evaluated using the Cochrane risk of bias tool as well as a funnel plot for publication bias, and quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Bias was largely uncertain; however, a high risk of bias was noted in four studies. No significant overall publication bias was noted. The quality of evidence was determined to be very low based on the GRADE tool, downgraded based on risk of bias, inconsistency, and imprecision. Despite the quality of evidence, the data were pooled in light of the current recommendations from the CDC to critically evaluate the recommendation that a single dose of antibiotics be utilized.

Results There were no differences in infection risk between single- versus multiple-dose groups (single: 83 of 4263 [2%], multiple: 101 of 5428 [2%]; odds ratio, 0.92 [95% confidence interval, 0.56-1.51]; $p = 0.740$, $I^2 = 36\%$ for statistical heterogeneity).

Conclusions There is no difference in infection risk between a single dose and multiple doses of perioperative antibiotics for orthopaedic procedures where implants are utilized, consistent with recent recommendations. However, the quality of evidence for orthopaedic procedures is low, and a randomized study with a sufficient sample size is needed to examine the issue before universal adoption of a single antibiotic dose.

Level of Evidence Level I, therapeutic study.

Introduction

The Centers for Disease Control and Prevention (CDC) recently published its updated guidelines for prevention of surgical site infection (SSI), which included a recommendation regarding perioperative antibiotic prophylaxis. Based on their evaluation of the available literature, the CDC recommended that a single dose of perioperative antibiotics be utilized for patients undergoing clean and clean-contaminated surgical interventions, advocating for no prophylaxis after the incision is closed in the operating room [5]. This guideline, which matches the recommendation from the World Health Organization (WHO) [30], encompasses surgeries in which implants are utilized, including arthroplasty, spine fusion, and fracture fixation. Furthermore, the CDC classified this as a category IA strong recommendation with high-quality evidence [5].

However, much of the literature cited by the WHO and CDC for this recommendation is based on cardiothoracic, vascular, and general surgeries, in which few or no implants are utilized [5, 32]. Although orthopaedic procedures were also evaluated and no difference in infection rate was noted, it is important to recognize that the surgical cohorts generating the majority of the evidence may behave differently from the orthopaedic patient population in terms of infection risk and severity of infection outcomes. In 2009, de Lissovoy et al. [11] reported an approximately 1% risk of SSI across all surgical specialties. Specifically, for orthopaedics, they reported a mean increase in hospital stay of 9.5 days for patients who developed SSI with cost of care averaging USD 15,129 more per patient, which was different from other surgical disciplines in their study [11]. When implants are involved, the cost of treating SSI is even greater with an average cost for periprosthetic joint infection (PJI) reported to be USD 74,900 in 2009 [5, 28]. These data suggest that orthopaedic infections are different from infections in other surgical disciplines. In light of the immense economic burden, and the added morbidity and mortality associated with management of infections surrounding an implant (including removal of hardware, infected nonunion, and explant and antibiotic spacer placement for PJI) [46, 47], it is pertinent to determine if a single dose of antibiotic prophylaxis is sufficient for prevention of these dreaded complications. Furthermore, this recommendation of a single dose is different from prior recommendations of discontinuation of antibiotics within 24 hours of surgery, creating unease from providers and hospitals [1, 42].

In light of the existing controversy, we asked: Is there is a difference in postoperative infection risk when utilizing a single dose of preoperative antibiotics compared with multiple doses of perioperative antibiotics for orthopaedic procedures where implants are placed?

Materials and Methods

Search Strategy and Criteria

A search for relevant articles was performed using the Preferred Reporting Items for Systematic Reviews and

Meta-analysis (PRISMA) guidelines, and the methodology outlined in the Quality of Reports of Meta-Analyses of Randomized Controlled Trials (QUOROM) statement was followed [33]. MEDLINE, EMBASE, Cochrane, and Google Scholar were queried for key terms of "single-dose antibiotic" and "orthopaedics" or "arthroplasty, spine, or fracture". Prospective randomized controlled trials (RCTs) from 1980 to 2017 of a single dose of antibiotics compared with multiple doses for infection prophylaxis in orthopaedic procedures where an implant was placed were included for analysis. Only manuscripts published in English were reviewed. Infection (both superficial and deep) as a primary outcome through all available followup was required for inclusion. In light of the changing definition of SSI over the years, all definitions of infection outlined by the authors were included. Studies without a control group receiving multiple doses of antibiotics were excluded in addition to all retrospective reviews. RCTs on different durations of postoperative antibiotics (that is, 2 days compared with 5 days) and studies pertaining to antibiotic prophylaxis for the removal of implants (resection arthroplasty or removal of fracture hardware) were also excluded. Additionally, the references from included full-text articles were reviewed for possible relevant studies. Articles were synthesized and reviewed through Covidence systematic review software (Melbourne, Victoria, Australia).

The search performed identified 1150 possible articles related to the subject matter of this study. After initial screening and removal of duplicate manuscripts, only 41 articles were felt to be relevant to answering the study question and were retained for full-text screening (Fig. 1). These articles were then narrowed to 14 RCTs that met these inclusion criteria. There was one additional manuscript directly comparing single versus multiple doses of antibiotics

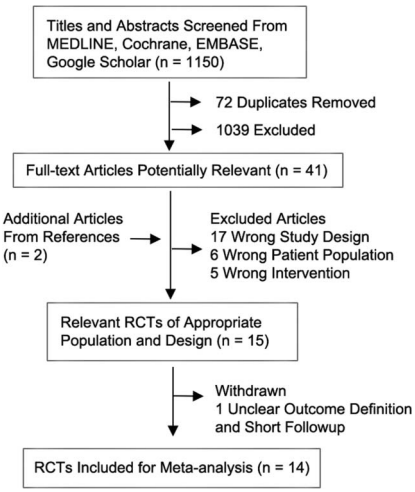

Fig. 1 A literature review for randomized controlled trials resulted in 14 studies for inclusion.

in a prospective randomized fashion that was excluded from analysis as a result of an unclear definition of "suspected infection" after only 10 days of followup [53]. Data were then extracted from the included articles by two of the authors independently (SPR, BJK). Relevant data included year of publication, patient population, sample size, antibiotic type and dosage, duration of followup, rate of infection, and authors' conclusions. Discrepancies in the data extracted were jointly reviewed and a consensus was reached before analysis. Unresolved differences were reviewed by a third author (TMS) for final inclusion. For the outcome analysis of postoperative infection, superficial and deep SSI were included, whereas other locations of infection (that is, pulmonary or urinary) were not considered relevant to our study question and were, therefore, not extracted for analysis.

Of the included manuscripts, there were seven articles specific to arthroplasty [22, 26, 34, 39, 41, 51, 54], one to spine [21], and six to general orthopaedic procedures that included the use of implants (two specific to hip fracture fixation) [8, 13-15, 27, 31]. The relevant studies included 9691 total orthopaedic patients (Table 1). Single-dose antibiotic agents investigated consisted of three studies using first-generation cephalosporins (cefazolin), five using second-generation cephalosporins (cefamandole, cefonicid, and cefuroxime), two administering third-generation cephalosporins (ceftizoxime and ceftriaxone), and four utilizing a synthetic glycopeptide (teicoplanin). Multiple-dose antibiotics were the same agent as the single-dose antibiotic in seven of 14 studies (50.0%) and included five manuscripts investigating first-generation cephalosporins (cefazolin), seven utilizing second-generation cephalosporins (cefamandole and cefuroxime), and two investigating third-generation cephalosporins (ceftizoxime and cefotaxime). One study used a wide variety of antibiotics in the multiple-dose group [26] and another used nafcillin or cefazolin [22]. The largest single study comparing the same antibiotic agent as a single versus multiple dose included 2651 patients from the Netherlands undergoing THA or hemiarthroplasty [54]. There was significant heterogeneity among antibiotic doses postoperatively among trials from a single postoperative dose [14, 51] to up to 10 days of antibiotics postoperatively [21]. The definition of infection was also variable across studies from the presence of purulent material, positive cultures, inflamed wounds, or a combination of pain, tenderness, fever, radiographic abnormalities, elevated inflammatory markers, or bone scan with atypical signs [8, 15, 22, 41, 51, 55]. Followup varied from 10 days [14] postoperatively to 2 years minimum [51] across studies.

Heterogeneity

I^2 statistic was utilized to determine study heterogeneity for subsequent meta-analysis. The thresholds provided by the

Table 1. Orthopaedic procedures with single versus multiple doses of perioperative antibiotic prophylaxis

Author, year	Country of study	Population and followup	Number of patients/ treatment	Infection results	Author conclusions
Gatell et al. [15], 1987	Spain	Population: all orthopaedic procedures with metal implant other than arthroplasty Followup: 1 year	N = 717 Group 1: 2 g cefamandole preoperatively and intraoperatively and then 1 g 8 hours, 14 hours, 20 hours postoperatively (N = 335) Group 2: single-dose 2 g cefamandole (N = 382)	Wound infections: -3 patients (0.9%) in Group 1 -20 patients (5.2%) in Group 2	Postoperative antibiotics reduced the rate of infection compared with a single preoperative dose
Buckley et al. [8], 1990	Canada	Population: orthopaedic hip fractures treated with hip pinning or hemiarthroplasty Followup: 6 weeks	N = 352 Group 1: 2 g cefazolin preoperatively and then 1 g every 6 hours for 3 doses (N = 108) Group 2: single-dose 2 g cefazolin (N = 83) Group 3: placebo control (N = 121)	Wound infections: -2 patients (1.6%) in Group 1 -2 patients (2.4%) in Group 2 -4 patients (3.7%) in Group 3 All infections superficial except one in Group 3	No significant difference between a single dose and multiple doses of prophylactic antibiotics; a larger cohort was recommended by the authors
Karachalios et al. [27], 1990	Greece	Population: fixation of intertrochanteric fractures Followup: 1 year	N = 200 Group 1: single-dose 1 g ceftriaxone (N = 99) Group 2: 1 g cefotaxime every 8 hours for 3 days (N = 101)	Deep infections -1 patient (1.0%) in Group 1 -1 patient (1.0%) in Group 2	Single dose of ceftriaxone is as effective as multiple doses of cefotaxime for preventing SSI
Garcia et al. [13], 1991	Spain	Population: all orthopaedic procedures with metal implant other than arthroplasty Followup: 13 months	N = 1489 Group 1: single-dose 2 g cefonicid (N = 474) Group 2: 3 doses (2 g preoperatively and then 1 g every 6 hours) cefamandole (N = 510) Groups 3: 5 doses (2 g preoperatively and then 1 g every 6 hours) cefamandole (N = 505)	Wound infections: -7 patients (1.5%) in Group 1 -10 patients (2.0%) in Group 2 -10 patients (2.0%) in Group 3	Similar infection rates are seen in all three groups; based on cost, a single dose or three doses should be used

Table 1. continued

Author, year	Country of study	Population and followup	Number of patients/ treatment	Infection results	Author conclusions
Garotta et al. [14], 1991	Italy	Population: implantation of a metallic device including fracture fixation and arthroplasty Followup: 10 days	N = 896 Group 1: single-dose 2 g ceftizoxime (N = 301) Group 2: 2 g ceftizoxime preoperatively and then 2 g at 12 hours (N = 313) Group 3: 2 g cefuroxime preoperatively and then 1 g every 8 hours for 48 hours (N = 282)	Wound infections -2 patients (0.66%) in Group 1 -3 patients (0.96%) in Group 2 -2 patients (0.71%) in Group 3	No significant difference in infection rate between a single dose and multiple postoperative doses
Liebergall et al. [31], 1995	Israel	Population: orthopaedic procedures with insertion of metal devices including fractures and arthroplasty Followup: mean 149.9 days Group 1, 173 days Group 2	N = 102 Group 1: single-dose. 1 g cefonicid (N = 54) Group 2: 1 g cefazolin every 8 hours for 16 hours (N = 48)	Wound infections: -0 in Group 1 -3 patients (6.3%) in Group 2	Single preoperative dose of cefonicid is not inferior to multiple doses of cefazolin
Arthroplasty-specific					
Heydemann and Nelson [22], 1986	USA	Population: hip and knee arthroplasty Followup: 1 year	N = 466 Group 1: single-dose 1 g cephazolin or nafcillin (N = 103) Group 2: 1 g cephazolin or nafcillin every 6 hours for 48 hours (N = 108) Group 3: 1 g cephazolin or nafcillin every 6 hours for 24 hours (N = 127) Group 4: 7 days of antibiotics (3 days intravenously and then 4 days orally) (N = 128)	Deep infections: -0 in Group 1 or 2 -1 patient (0.78%) in Group 3 -2 patients (1.6%) in Group 4	A single dose may decrease both complications and costs without increasing SSI

Table 1. continued

Author, year	Country of study	Population and followup	Number of patients/ treatment	Infection results	Author conclusions
Ritter et al. [41], 1989	USA	Population: primary hip and knee arthroplasty Followup: 1 year	N = 196 Group 1: intraoperative cefuroxime (2 doses: 1500 mg and 750 mg) (N = 98) Group 2: 750 mg cefuroxime every 8 hours for 24 hours (N = 98)	Deep infections: -0 patients in either group	No difference was seen between groups; intraoperative prophylaxis alone without postoperative doses may be adequate for prevention of SSI
Wymenga et al. [54], 1992	Netherlands	Population: total hip and hemiarthroplasty Followup: mean 13 months	N = 2651 Group 1: single-dose 1.5 g cefuroxime (N = 1327) Group 2: 1.5 g cefuroxime intraoperatively and then 750 mg every 8 hours for 2 doses (N = 1324)	Joint sepsis: -11 patients (0.83%) in Group 1 -6 patients (0.45%) in Group 2 Wound infection: -25 patients (1.88%) in Group 1 -31 patients (2.34%) in Group 2	Despite no significant difference between groups, the authors recommended continuing a multiple-dose regimen until a larger study could be performed
Mollan et al. [34], 1992	United Kingdom	Population: primary total hip and knee arthroplasty Followup: 30 days	N = 660 Group 1: single-dose 400 mg teicoplanin (N = 308) Group 2: 2 g cefamandole preoperatively and then 1 g every 6 hours for 18 hours (N = 352)	Infection failure: -2 patients (0.65%) in Group 1 -3 patients (0.85%) in Group 2	There is no significant difference in SSI between single-dose teicoplanin and multiple doses of cefamandole
Suter et al. [51], 1994	Italy	Population: primary THA Followup: 2 years	N = 496 Group 1: single-dose 400 mg teicoplanin (N = 250) Group 2: 2 g cefamandole preoperatively and then 1 g postoperatively (N = 246)	Wound infections: -0 in Group 1 -4 patients (1.6%) in Group 2	No significant difference between groups; a single dose of teicoplanin is safe in preventing SSI compared with multiple doses of cefamandole

Table 1. continued

Author, year	Country of study	Population and followup	Number of patients/ treatment	Infection results	Author conclusions
Periti et al. [39], 1999	Italy	Population: total hip and knee arthroplasty	N = 826	Wound Infections:	A single preoperative dose was not significantly different from multiple doses of prophylaxis
		Followup: 1 year	Group 1: single-dose 400 mg teicoplanin (N = 410)	-6 patients (1.5%) in Group 1	
			Group 2: 2 g cefazolin preoperatively and then 1 g every 6 hours for 24 hours (N = 416)	-7 patients (1.7%) in Group 2	
Kanellakopoulou et al. [26], 2009	Greece	Population: primary total hip and knee arthroplasty	N = [illegible]	Infection:	A single dose of teicoplanin has a significantly lower rate of infection compared with multiple prophylactic doses of other antibiotics
		Followup: 2 years	Group 1: single-dose 10 mg/kg teicoplanin (N = 256)	-2 patients (0.78%) in Group 1	
			Group 2: 4-6 days of antibiotics (various antibiotics with different dosing regimens) (N = 312)	-11 patients (3.53%) in Group 2	
Spine-specific					
Hellbusch et al. [21], 2008	USA	Population: instrumented lumbar fusions	N = 233	Superficial infections:	No significant difference in SSI with a single dose compared with extended prophylaxis; the authors note a larger study is suggested
		Followup: unknown	Group 1: single-dose 1-2 g cefazolin (N = 117)	-5 patients (4.3%) in Group 1	
			Group 2: 3 days 1-2 g cefazolin every 8 hours and then 7 days 500 mg cephalexin (N = 116)	-2 patients (1.7%) in Group 2	

All studies present were included for data analysis; SSI = surgical site infection.

Cochrane group were utilized for determining I^2 thresholds, whereby 30% to 60% indicates moderate heterogeneity and > 60% indicates substantial heterogeneity [24]. After data collection, I^2 was found to be 36% for the available 14 RCTs. Furthermore, given the heterogeneity in the definition of infection as well as the antibiotics utilized, the studies were not identical in form. Given the clinical and statistical heterogeneity noted, random-effects modeling was utilized for statistical analysis.

Publication Bias

Publication bias was assessed visually with a funnel plot for the primary outcome using ProMeta Version 3.0 (Cesena, Italy: IDoStatistics-Internovi). This plot allowed comparison of each individual study's treatment effect against the study precision (Fig. 2). Relative symmetry of the study distribution around the pooled effect size estimate (denoted by the vertical line) was noted, indicating a low probability for publication bias. This observed symmetry was supported by an Egger's regression test, which evaluated the degree of plot asymmetry and was not statistically significant ($p = 0.497$).

Quality Assessment

Two reviewers (SPR, BJK) independently assessed each article for bias using the Cochrane risk of bias tool through Covidence, and discrepancies were resolved through consensus. The Cochrane risk of bias tool includes multiple facets of bias assessment including selection bias (from inadequate randomization or allocation concealment), performance and detection bias (including blinding of participants and investigators), attrition bias (including incomplete outcome data), reporting bias (from incomplete outcomes reported and selective reporting), and "other" sources of bias. Utilizing the Cochrane bias assessment, two studies showed unclear bias in all categories given the lack of sufficient detail regarding the randomization process, allocation concealment, blinding, data reporting (including attrition bias and reporting bias), and other sources of bias (Fig. 3). Wymenga et al. [55] reported the largest series of patients; however, they had no blinding of participants, and randomization was performed in groups of 10 patients, creating high levels of bias in allocation concealment and blinding. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool was subsequently used to determine the quality of evidence derived from the available RCTs [18, 20, 43]. GRADE scores (including upgrading [+1 or +2] and downgrading [-1 or -2] evidence) were determined independently and agreed on through consensus of two authors (SPR, BJK) after thorough review of the studies in accordance with the Cochrane study guidelines [43]. Using this tool, the quality of evidence was downgraded from high (RCTs) to very low (Table 2) as a result of bias, inconsistency resulting from the variability of antibiotic type, duration, and definition of infection, and imprecision attributable to inadequate power.

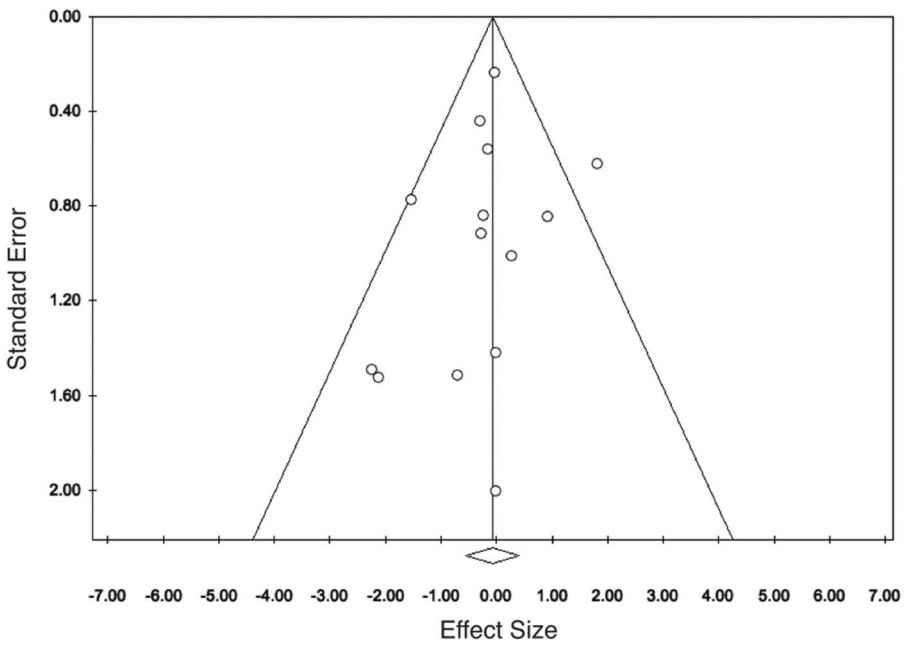

Fig. 2 The funnel plot for publication bias shows relative symmetry around the overall effect size, demonstrating a lack of bias.

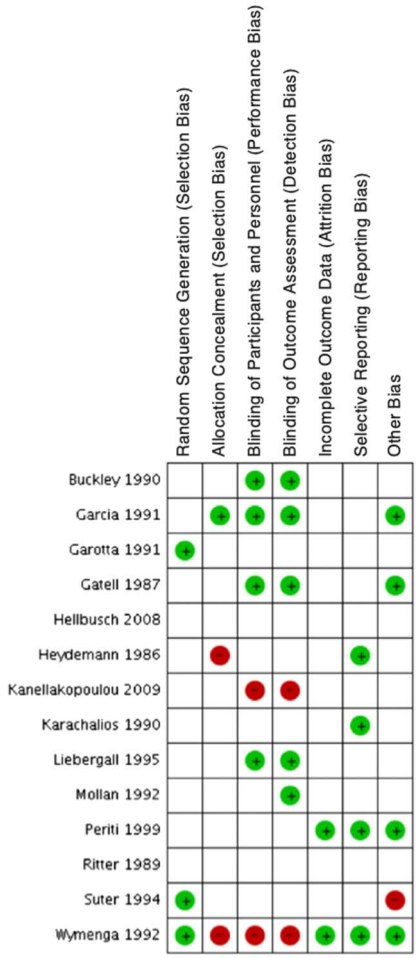

Fig. 3 The risk of bias of the available literature based on the authors' judgment about each risk of bias item for the included studies is summarized. Blank = uncertain risk; (+) = low risk; (-) = high risk.

Data Synthesis and Analysis

Despite the low quality of evidence, it is important to determine the overall findings of the pooled data, which has not previously been reported for this cohort of patients and may differ from that of other surgical disciplines that formed the CDC's recommendations. Infection risk, as reported by the authors of relevant articles, was considered a dichotomous variable for analysis. Although there was moderate statistical and clinical heterogeneity present across RCTs in the definition and reporting of "infection risk," from independent reporting of superficial and deep infections (which were combined for data analysis) to only reporting wounds with purulent drainage, individual studies reporting "infection risk" were considered homogenous. The binary outcome of infection versus no infection was combined across all studies and analyzed with a Mantel-Haenszel method using random-effects modeling, as previously noted. Two subanalyses were then performed for (1) the largest cohort of similar procedures, which consisted of seven arthroplasty-specific studies; and (2) 10 studies with low or unclear bias, excluding studies with high bias (Fig. 3). The data are presented as odds ratios (ORs) with 95% confidence intervals (CIs) and a forest plot was used to illustrate the infection outcomes of the included studies. This was created through Review Manager 5.3 (Copenhagen, Denmark: Nordic Cochrane Center, Cochrane Collaboration).

Table 2. GRADE summary of outcome quality of evidence

Outcome	Rating	Notes
Study design	+4	Randomized controlled trials
Risk of bias	-1	Bias mostly unclear from the available trials (Fig. 3)
Inconsistency	-1	Variable antibiotic selection and duration for "multiple-dose" groups; variable definition of infection; moderate heterogeneity in results
Indirectness	0	
Imprecision	-1	Underpowered studies; rare complication with few events available for analysis
Publication bias	0	
Overall rating	+1	Very low quality of evidence

Ratings based on author consensus from the Cochrane guidelines are shown; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

Results

The pooled data analysis showed no differences in infection risk between single- versus multiple-dose groups (single: 83 of 4263 [1.9%], multiple: 101 of 5428 [1.9%]; OR, 0.92 [95% CI, 0.56-1.51]; p = 0.740, I^2 = 36% for statistical heterogeneity; Fig. 4). Two separate subanalyses were then performed. First, the arthroplasty cohort, which included seven RCTs, was independently analyzed and similarly showed no difference in infection outcome between a single and multiple doses of perioperative antibiotics (single: 46 of 2752 [1.7%], multiple: 65 of 3111 [2.1%]; OR, 0.74 [95% CI, 0.45-1.22]; p = 0.240). Second, the four studies showing high bias utilizing the Cochrane risk of bias tool were excluded, leaving 10 RCTs with unclear or low bias. These studies showed no difference in infection outcome between single and multiple doses of antibiotics (single: 45 of 2327 [1.9%], multiple: 46 of 3183 [1.4%]; OR, 1.19 [95% CI, 0.63-2.24]; p = 0.590).

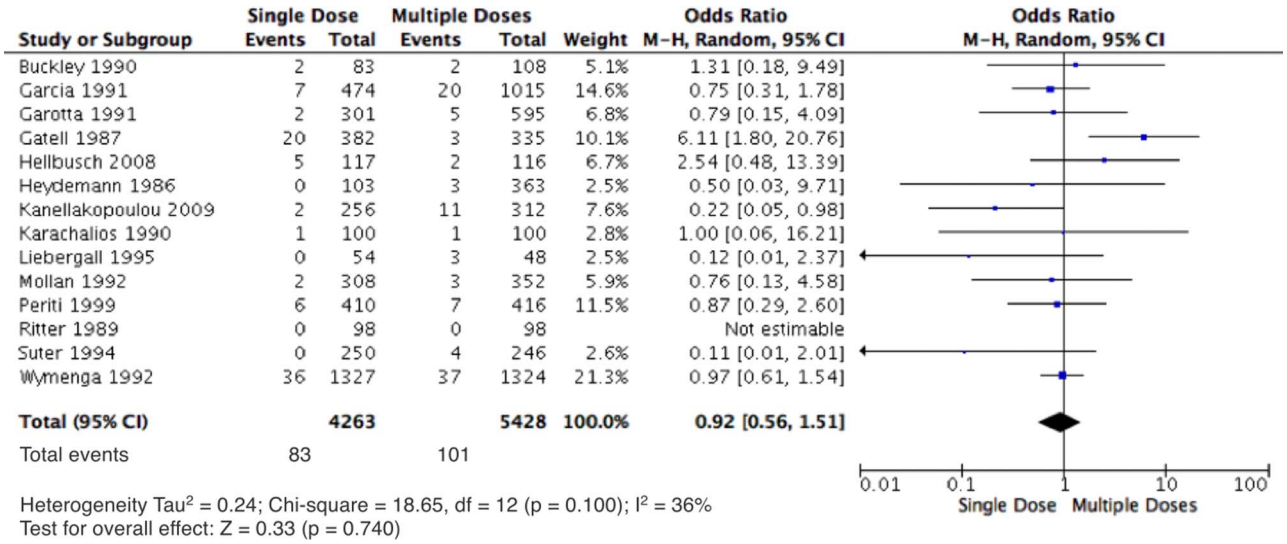

Fig. 4 The pooled results of the effect of a single versus multiple doses of postoperative antibiotics for orthopaedic procedures where implants are utilized demonstrates no significant difference in infection rate. M-H = Mantel-Haenszel.

Discussion

The CDC and WHO have recently recommended that only a single dose of preoperative antibiotics be administered for all clean and clean-contaminated procedures, including arthroplasty, fracture fixation, and spine fusion procedures [6, 30]. Withholding postoperative antibiotics is in contrast to prior recommendations in 2006 from the Surgical Care Improvement Project (SCIP), which recommended discontinuation of antibiotics within 24 hours of surgery [44]. The lack of recent studies specific to orthopaedics has led to controversy surrounding this recommendation, and the American Association of Hip and Knee Surgeons (AAHKS) released a position statement against adopting a single dose for perioperative prophylaxis at this time [1, 52]. Therefore, we aimed to determine if a single dose of preoperative antibiotic prophylaxis is equivalent to multiple doses for postoperative infection prophylaxis and to critically evaluate the available evidence for orthopaedic procedures where implants are placed. We found that a single dose of perioperative antibiotics is no different compared with multiple doses for prevention of postoperative infections when implants are used during the procedure. The quality of available evidence for orthopedic surgery is, however, poor compared with other surgical disciplines that formed the basis for the CDC and WHO recommendation of a single preoperative dose of antibiotics [5, 30].

There are several limitations to the results of this study: that a single preoperative dose of antibiotics has equivalent infection prophylaxis as multiple doses. First, many of the studies were conducted in the late 1980s and early 1990s given the broad date range for inclusion. Since that time, additional strategies for infection prophylaxis and aseptic technique may limit the value of additional doses of antimicrobials postoperatively. However, even with their inclusion, no difference in infection rate was noted, thereby strengthening our results. Many of the remaining limitations are evident from very low quality of evidence determined by the GRADE quality assessment tool, which was downgraded secondary to heterogeneity as well as a lack of study power. Regarding the inconsistency and heterogeneity, the definition of SSI and antibiotic selection was variable throughout studies, as previously mentioned. Although some authors required a positive culture to be considered an infection [22], others included different combinations of inflammatory markers, pain, radiographic findings, and erythema in their infection diagnosis [8, 15, 41, 51, 54]. However, these definitions were not consistent with the CDC or Musculoskeletal Infection Society (MSIS) criteria for infection, which were largely adopted after many of these studies were conducted, highlighting the need for a universal definition of infection [35, 38, 49]. Furthermore, the antibiotics utilized were variable not only across studies, but within individual trials comparing single with multiple antibiotic doses. The most commonly utilized single-dose antimicrobial was teicoplanin, a synthetic glycopeptide with Gram-positive coverage (including methicillin-resistant *Staphylococcus aureus*) that is similar to vancomycin; however, it is unavailable in some regions, including throughout the United States [36]. Other antibiotics utilized were largely not reflective of the current practice in Canada and the United States, where cefazolin is the most frequently utilized first-line prophylactic agent for both arthroplasty and fracture fixation [10, 12]. Later generations of cephalosporins have broader coverage than

Table 3. Organization recommendations for duration of antibiotics in orthopaedics

Organization	Recommendation	
	Discontinue antibiotics within 24 hours	Discontinue antibiotics after incision closure
Surgical Infection Prevention Project, 2002 [3]	✓	-
National Institute for Health and Care Excellence, 2008 [29, 50]	-	✓
UK Department of Health, 2011 [23]	-	✓ with exceptions‡
Surgical Care Improvement Project, 2011 [42]	✓	-
Royal College of Physicians of Ireland, 2012 [40]	Arthroplasty, head and neck surgery	✓ with exceptions†
British Orthopaedic Association, 2012 [7]	✓	Debated
Musculoskeletal Infection Society, 2013 [37]	✓	-
American Society of Health-System Pharmacists, 2013 [6]	✓	Debated
North American Spine Society, 2013 [45]	Debated	Debated
American Academy of Orthopaedic Surgeons, 2014 [25]	✓	-
Society for Healthcare Epidemiology of America, 2014 [3]	✓	-
World Health Organization, 2016 [17, 30]	-	✓
South African Orthopaedic Association, 2016 [19]	✓	-
American College of Surgeons, 2016 [4]	-	✓ with exceptions*
Center for Disease Control, 2017 [5]	-	✓
American Association of Hip and Knee Surgeons, 2017 [1]	✓	Not until further study
Southern Australian Advisory Group on Antibiotic Resistance, 2017 [48]	-	✓
Orthopaedic Trauma Association, 2018 [2]	✓	-

*Except arthroplasty, cardiac procedures, and implant-based breast reconstruction.
†except arthroplasty, head and neck surgery, implant surgery of the mandible, orthognathic surgery, complex septorhinoplasty.
‡except arthroplasty.

cefazolin; however, when looking at cefamandole, which was utilized in four studies as a multiple-dose prophylaxis, the half-life is approximately half that of cefazolin [9]. Therefore, a comparison of two different antibiotics within one study, or of antibiotics different from those most commonly utilized in the United States, may not be reflective of many practitioners influenced by the previously mentioned studies. Additionally, there was a broad international distribution of patients across studies (United States, Spain, Canada, Greece, Italy, Israel, Netherlands, United Kingdom), which all have different standards of reporting, and it has previously been noted that factors associated with SSI and readmission differ across countries [16]. We feel this further contributed to study heterogeneity, although it is critical to include all of these studies because the WHO and CDC are making recommendations for all countries around the world. The noted heterogeneity led us to analyze the data with random-effects modeling, allowing us to partially account for this limitation through our analysis, thereby strengthening our results and making them most reflective of the existing literature.

Regarding the noted imprecision, none of the available studies were powered to detect a difference in the risk of infection. As an example, if the postoperative infection rate in orthopaedics is 1% to 2%, a cohort of 3500 patients per group (7000 patients total) would be required in a single study to detect a difference between the treatments of interest (single versus multiple doses of antibiotics). None of the studies to date have included this sample size, and several contained fewer than 100 patients per group. Thornley et al. [52] in a prior meta-analysis that was specific to arthroplasty included 4036 total patients across four RCTs, which remains underpowered to detect a significant difference in infection rate [52]. However, by pooling all of the available studies identified, we were able to achieve a cohort of sufficient size to detect a difference in infection rate, should one exist. Therefore, despite the limitations to the available data, our pooled analysis provides the first evaluation of a single dose of antibiotics compared with multiple perioperative doses specific to orthopaedic procedures where implants are being placed. To our knowledge, this is the first study of its kind with a sufficient sample size to identify a difference in postoperative infection rate.

Although pooled data demonstrate no differences in infection risk between single versus multiple antibiotic doses,

because of the low quality of evidence, we caution against immediate implementation. Our results agree with the CDC and WHO recommendations; however, the high-quality evidence cited by these organizations was largely derived from other surgical disciplines where metallic implants are not being placed and surgical infections are treated very differently. The lack of clarity regarding the available evidence specific to orthopaedics has led many societies around the world to provide different recommendations for the optimal duration of perioperative antibiotic prophylaxis with several organizations making exceptions for a single preoperative dose for arthroplasties or when implants are placed (Table 3). Furthermore, the AAHKS Research Group has recently funded a multicenter randomized controlled trial with the aim of including enough patients to achieve sufficient power to investigate infection prophylaxis using a single versus multiple antibiotic doses. This highlights the importance of answering this question specifically in orthopaedics before universal adoption. Therefore, although the current evidence provided by this study is the best available evidence to date and suggests equivalent prophylaxis, immediate implementation of a single dose without appropriate surveillance could have unforeseen consequences and further study is encouraged.

Conclusion

Currently, the best available data suggest that a single preoperative dose of antibiotics offers equivalent infection prophylaxis when compared with multiple perioperative doses for orthopaedic procedures where implants are placed. However, the quality of evidence is low, and a randomized study with a sufficient sample size is needed to examine the issue before universal adoption.

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