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The effect of timing of antibiotic delivery on infection rates related to open limb fractures: a systematic review

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WHAT THIS PAPER ADDS

What is already known on this subject

Open fractures are severe injuries that are at high risk of infection when compared to other types of fracture. Antibiotics have been shown to reduce the risk of infection when compared to placebo or no antibiotics. It is not known whether the timing of delivery of antibiotics influences the risk of infection following open fractures.

What this study adds

Our systematic review demonstrates a lack of robust evidence to determine whether there is a benefit associated with the early delivery of antibiotics in open fractures. In order to establish whether resources should be devoted to achieving earlier delivery of antibiotics in these patients, a randomised controlled trial is required.

ABSTRACT

Objective: To examine whether the timing of delivery of intravenous antibiotics following open limb fractures has an effect on deep infection rates and other outcomes.

Design: We published an a priori study protocol in PROSPERO. Our search strategy combined terms for antibiotics, timing of administration and fractures. Two independent reviewers screened, selected, assessed quality and extracted data from identified studies.

Data sources: We searched five electronic databases with no limits and performed grey literature searches.

Eligibility criteria for selecting studies: Randomised, non-randomised controlled studies, prospective and retrospective observational studies in which the effect of the timing of delivery of antibiotics on the outcome of deep infection in open fractures was considered were included.

Results: Eight studies were included according to the above criteria. There were no randomised or non-randomised controlled trials. None of the included studies provided data on patient reported or health related quality of life. The overall deep infection rate ranged from 5-17.5%. All of the studies were at substantial risk of bias. One study reported a reduced infection rate with the delivery of antibiotics within 66 minutes of injury and seven studies reporting no effect.

Conclusions: There is not currently sufficiently robust evidence available to determine whether the timing of delivery of intravenous antibiotics has an effect on the risk of deep infection or other outcomes following open limb fractures. There is therefore a need for a randomised controlled trial in this area before policy changes should be instigated.

Review registration number: PROSPERO (CRD42015016729)

INTRODUCTION

An open fracture is a break of a bone that communicates with the environment through a breach in the skin. The annual incidence of open long bone fractures is 11.5 per 100,000 persons per year and over 70% involve the lower limb.[1,2] When an open fracture occurs, the barrier provided by the skin is lost, leading to an increased risk of infection.

Open fractures are most commonly graded according to the Gustilo and Andersen classification.[3,4] This is applied at the time of surgery and uses a 1 to 3 scale according to the size of the wound. Grade 3 fractures are further divided according to the complexity of reconstruction needed. The risk of infection is 0-7% for grade 1, 0-11% for grade 2, 2-36% for grade 3 and up to 44% for the grade 3C subtype.[3-15] Infection rates of 27% following grade 3 fractures are typical even in contemporary specialist centres.[16] The consequences of developing an infection are significant, leading to prolonged pain, decreased function, the need for prolonged antibiotics and further surgical interventions or amputation. The associated health care costs are £105,000 if the limb can be salvaged and £320,000+ if amputation is required. This is a fraction of the subsequent personal and societal cost.[17]

Current national standards of care typically state that antibiotics should be given as soon as possible after an open fracture occurs[18] but in most cases, antibiotics are not given until the patient arrives in hospital meaning there can be a substantial delay between injury and receiving antibiotics. There is some evidence that if antibiotics can be delivered within 66 minutes of injury, the subsequent deep infection rate may be decreased.[6] Delivery of antibiotics by prehospital providers or clinicians reduces the time to delivery of antibiotics in this cohort and the diagnostic accuracy in this setting is over 95%.[2]

There is currently no definitive trial or systematic review in this area. The aim of this systematic review was to assess whether the timing of delivery of intravenous antibiotics in patients following open limb fractures had an effect on the outcomes of treatment including the incidence of deep infection, patient reported outcomes and health related quality of life.

METHODS

A protocol for the systematic review was developed and registered with PROSPERO (International prospective register of systematic reviews; registration number CRD42015016729) prior to commencing the review.

Search Strategy

An information specialist searched the following databases from 1980 to 17th February 2015: Medical Literature Analysis and Retrieval System Online (MEDLINE) and MEDLINE In-Process; Cochrane Central Register of Controlled Trials (CENTRAL); Excerpta Medica database (EMBASE); Conference Proceedings Citation Index- Science (CPCI-S) Science Citation Index Expanded (SCI - EXPANDED); Clinical Trials.gov; and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP).

The base search strategy was constructed using MEDLINE and then adapted to the other resources searched. Appendix 1 provides the search strategy used for MEDLINE. The search included terms for the following components: antibiotics AND timing of administration AND fractures. No language limits were used. An initial experiment was carried out to ascertain the usefulness of using terms for the names of individual antibiotics. It was determined that no additional useful material was likely to be gained and therefore the final strategy was based on a comprehensive use of index terms and the use of general terms for antibiotics.

The results of all searches were imported into Endnote XVII (Thomson Reuters, CA, USA) bibliographic software and de-duplicated. Two authors (MW and CMcD) screened the bibliographic references in Endnote based on the review eligibility criteria. The full texts of any potentially relevant citations were ordered and independently screened. Disagreements were resolved through discussion. Where there were papers related to the same cohort the most comprehensive paper was included.

Study selection

Studies were assessed for eligibility against the following criteria:

Population - People of any age who have an open limb fracture of any severity.

Intervention - Studies investigating timing of administration of IV antibiotics given prophylactically, including studies comparing prehospital antibiotic administration to administration in the emergency department.

Comparator - Prophylactic IV antibiotics provided at a different time. Studies comparing different antibiotics or other aspects of regimen were excluded.

Outcome – Infection or deep infection rates, patient function, quality of life (using standardised patient reported outcome measures), fracture union, amputation, mortality and indicators of infection including unscheduled operative procedures, number of operative procedures, need for further IV antibiotics and number and type of adverse events and serious adverse events.

The primary outcome of interest was deep infection associated with the open fracture wound. Given the exploratory nature of the review, the definition of deep infection associated with open fracture wound, used by individual studies, was accepted.

Study design - Randomised controlled trials (RCTs) were eligible for inclusion. In the absence of this study design, non-randomised controlled studies and prospective and retrospective observational designs were included provided timing of antibiotic delivery was investigated.

Data extraction and assessment of study quality

A data extraction form was developed and piloted. Data extracted included details of objectives, study design, setting, eligibility criteria, participant characteristics, details of timing of antibiotic, other variables investigated and results for the outcomes of interest for the comparison on the timing of delivery of antibiotics. Data were extracted and the quality of studies assessed by one researcher and checked by a second. We planned to use the Cochrane Risk of Bias Tool[19] to assess risk of bias in included RCTs and quasi RCTs and The Newcastle-Ottowa scale to assess observational study designs.[20] Following piloting we found the latter of limited utility for the uncontrolled study designs we included. We therefore used a list of criteria based on a previous review of uncontrolled studies.[21] Appendix 2 provides details of the criteria and appendix 3 the results of the risk of bias assessment.

Synthesis

The key aim of the synthesis was to identify gaps in the evidence and identify implications for future research. As specified in the pre-registered protocol we did not undertake a meta-analysis due to the absence of RCTs. None of the studies identified were robust study designs to address the research question and were at considerable risk of bias. Any pooled estimate of the available results would therefore be unreliable and potentially misleading. In addition there was considerable heterogeneity within the non-randomised study designs that were identified (for example in how infection was defined, the diagnostic threshold used, the use of non-validated diagnostic criteria, how the timing of delivery of antibiotics was defined and whether data were gathered retrospectively or prospectively). It is difficult to predict how this bias and heterogeneity would influence the direction of the effect estimate generated by pooling of data. There is conflicting evidence from methodological work on non-randomised study designs whether the effect is over- or underestimated when compared to RCTs.[22] It is suggested that the main effect is one of uncertainty in the estimate over and above that accounted for in the confidence intervals. Pooling of data would therefore not be justified or reliable therefore a narrative description of the included studies is provided.

RESULTS

Study selection

The searches identified 670 citations, following de-duplication. Titles and abstracts were screened for potentially eligible studies and 24 full papers obtained and assessed for inclusion against the eligibility criteria (Figure 1). Eight studies were included.[2,6,12,23-27] Three studies[28-30] were excluded because they were abstracts reporting on the same cohort as an included study; one because it was a reply to a letter related to an included study;[31] and the remaining 12 studies did not meet at least one inclusion criterion.[15,16,32-41]

Overview of included studies

Table 1 provides a summary of the included study characteristics with full data extraction tables available in Appendix 4 (supplementary file). The searches did not identify any RCTs or non-randomised controlled studies. Five were prospective cohorts and three retrospective with a total of 2,142 participants. Study size ranged from 89 to 736, though fewer than this were included in individual analyses.

The studies were based in the United Kingdom (UK);[25,27] Australia;[26] Canada and/or the United States of America (USA).[2,6,12,23,24] The oldest study was approximately 30 years old with the cohort running from 1983 to 1986[12] the most recent ran from 2010 to 2013.[6] Three studies restricted the eligible open fractures to the tibia[6,26] or radius and/or ulna[23] whereas the remaining studies included a wider range of open fractures. The proportion of participants in studies with Gustilo-Anderson grade I or II ranged from 0%[6] to 72%.[12]

All of the included studies assessed our primary outcome of interest, deep infection, however there was considerable variability in how this was defined and one study reported it as part of a composite outcome.[2] The other most commonly reported outcome was fracture non-union.[12,23,26] None of the studies reported measures of patient function or quality of life and our other outcomes of interest were only reported by single studies (Appendix 4), and not explored by time of antibiotic administration. Only one study explicitly investigated the effect of prehospital administration of antibiotics.[2]

Table 1 Summary of study characteristics

Publication details, Setting, time period of study	Study design Duration of follow-up	Population Eligibility criteria, fracture severity	Number of participants	Details of antibiotic intervention	Definition of deep infection	Quality assessment
Al-Arabi (2007)[27] **Setting** UK; single general hospital (without onsite plastic surgery) **Time period** April 1996 to 2005 Two separate phases. Data on antibiotics (n=133) from 2000 to 2005 only	Prospective cohort, Consecutive selection **Duration of follow-up** Until radiological union or non-union was confirmed	All open fractures, any age. Excluded patients who died within 3 months of injury or transferred to a specialist unit for definitive treatment **Gustilo-Anderson Grade** 1, 31%; II, 22%; IIIA, 26%; IIIB, 21%	N=294 N=237 (248 fractures) included in analyses; n=133 in analysis of timing of antibiotic administration Excluded 3 due to death within 3 months, 54 transfer to another centre for definitive treatment	**Timing definition** Time from injury. Classified as <2, 4, 6, 8, 12 and >12 hours **Type and regimen** IV cefuroxime 1g (plus 500mg metronidazole for heavily contaminated wounds)	Diagnosed clinically based on swelling, erythema, discharging wounds and pain, and where possible confirmed with cultures	A = Y B = N C = Y D = Y E = Y F = N G = Y H = P I = N J = N
Dellinger (1988)[12] **Setting** Canada and USA; three hospitals **Time period** 1983-1986	Prospective cohort, Consecutive selection **Duration of follow-up** >6months 78% (n=88); <6 months 22% (n=52)	Open fracture of humerus, radius, ulna, femur, tibia or fibula, ≥ 14 years old, antibiotics within 12 hours of injury, operative debridement within 24 hours and ≥21 days follow-up **Gustilo-Anderson Grade** I, 25%; II, 47%; IIIA, 19%; IIIB, 5%; IIIC, 5%	N=240 (263 fractures)	**Timing definition** Time from injury. Classified as ≤3 or >3 hours **Type and regimen** IV cefonicid sodium 2g, cefamandole nafate 2g or cefazolin with varying follow-up regimens	Involvement of tissues below the muscular fascia (acute if resolved within 4 week period after diagnosis after one continuous course of antibiotics and operative procedures; chronic if exceeded four week duration)	A = Y B = Y C = U D = Y E = Y F = N G = N H = P I = N J = P

Enninghorst (2011)[26] **Setting** New South Wales, Australia; Level 1 trauma centre **Time period** 1 January 2007 to 31 December 2009	Prospective cohort, Consecutive selection **Duration of follow-up** 12 months	**Eligibility criteria** Age >18, blunt trauma patients with open tibia shaft fractures **Gustilo-Anderson Grade** 1, 25%; II, 30%; III, 45% (n=40) (IIIa, 20%; IIIb, 24%; IIIc, 1%)	N=89	**Timing definition** Not stated **Type and regimen** Not stated	Infection requiring surgical debridement and long-term IV antibiotics based on infectious disease service consultation	A = Y B = Y C = U D = Y E = N F = N G = Y H = P I = Y J = Y
Lack (2015)[6] **Setting** USA; Level 1 trauma centre **Time period** 1 December 2010 to 31 January 2013	Retrospective cohort, Consecutive selection **Duration of follow-up** 90 days	Gustilo-Anderson type III open tibia fractures with data for injury, antibiotic timing and 90 day outcome data (OTA 41, 42 and 43) **Gustilo-Anderson Grade** IIIa, 52%; IIIb/c, 48%	N=137 Excluded 13 for missing injury classification or antibiotic time; 9 non-reconstructible limb; 3 no 90 day outcome	**Timing definition** Time from injury. Used Receiver operator characteristic (ROC) curves to determine the threshold predictive of infection (≤66 or >66 minutes) **Type and regimen** Cefazolin received by 93.4% of participants. Continued for 24 hours postoperatively	Deep infection within 90 days of injury based on Centers for Disease Control criteria	A = Y B = Y C = Y D = N E = Y F = N G = Y H = Y I = Y J = Y
Leonidou (2014)[25] **Setting** UK; single hospital **Time period** 1 January 2006 to 31 December 2011	Retrospective cohort, Consecutive selection **Duration of follow-up** Until clinical or radiological union or a secondary procedure for non-union or infection was performed	All open long-bone fractures. Patients who died within 3 months of injury or who required transfer to a level 1 trauma centre for definitive treatment were excluded **Gustilo-Anderson**	N=212 patients, 220 fractures N=161 fractures and patients included in analysis) Excluded 2 due to death within 3 months; 27 transfer to level 1 trauma	**Timing definition** Classified according to whether antibiotics were received ≤ 3 or 3 hours post injury **Type and regimen** Cefuroxime and metronidazole until August 2008; co-amoxiclav from September 2008	Horan criteria. Purulent drainage from the deep incision; deep abscess formation; fascial dehiscence by the infection or during reoperation; deep infection in the presence of a metallic implant	A = Y B = N C = N D = N E = N F = Y G = N H = P I = P J = N

		Grade 1, 37%; II, 20%; IIIA, 25%; IIIB, 19%	centre; 17 lost to follow-up; 13 errors in data collection		around bone	
Thomas (2013)[2] **Setting** USA; 8 helicoptor emergency medical services (HEMS) **Time period** July 2009 to June 2010	Prospective cohort, Consecutive selection **Duration of follow-up** 6 months	Patients of all ages with a prehospital HEMS diagnosis of open fracture in any extremity being transported by any of the 8 participating HEMS. **Gustilo-Anderson Grade** Not stated	N=138 (132 had confirmed open fractures) N= 83 patients (from 5 services) in analysis Excluded 55 due to no final outcome data available	**Timing definition** Time from injury (assumption made that antibiotic was administered within 5 minutes of arrival in hospital group) **Type and regime** IV ceftriaxone, 1g	Any diagnosis of fracture site wound infection (regardless of depth or timing) Not measured as a single outcome. Used composite outcome of fracture site infection or non-union within 6 months	A = Y B = Y C = Y D = Y E = Y F = N G = N H = N I = N J = Y
Weber (2014)[24] **Setting** Canada; three level 1 trauma centres **Time period** 2001 to 2009	Prospective cohort, Consecutive selection **Duration of follow-up** One year (telephone interviews) or clinical follow-up of at least 90 days after surgery with a definitive clinical outcome recorded.	Skeletal maturity, long bone open fracture (humerus, radius/ulna, femur, tibia/fibula) and presenting for initial surgical debridement **Gustilo-Anderson Grade** 1, 29%; II, 37%; IIIA, 21%; IIIB, 12%; IIIC, 1%. No grade available in n=9.	**Number of participants** N=736 (791 fractures) N=686 (737 fractures) in analysis Excluded 50 due to missing outcome data	**Timing definition** Unclear **Type and regimen** Type I fractures: cefazolin (clindamycin if penicillin allergy). Type II and III: as above + gentamicin. Grossly contaminated fractures: as above plus penicillin	Infection requiring unplanned surgical debridement and/or sustained antibiotic therapy following definitive wound closure (confirmed through clinical records)	A = Y B = Y C = Y D = Y E = Y F = N G = N H = P I = P J = Y
Zumsteg (2014)[23] **Setting** USA; Level 1 trauma centre	Retrospective cohort, Consecutive selection **Duration of follow-up** At least 6 months	≥ 18 years old with open fracture of the radius and/or ulna (ICD9 codes). Excluded if inadequate	N=296 N=200 included in analysis Excluded: 91 patients	**Timing definition** Time from injury. Classified as ≤3hours or >3 hours **Type and regimen** Type I and II fractures: 2g	An infection requiring operative debridement according to patient notes (n=149) or telephone call to	A = Y B = Y C = Y D = N E = N F = N

Time period 1 January 2006 to 31 December 2011	(n=149) (though patients with shorter follow-up were included in the analysis for deep infection if data could be obtained by telephone contact, n=51)	information in the medical record, accurate information on time of injury not available, ballistic injury or traumatic amputation. **Gustilo-Anderson Grade** 1, 24%; II, 24%; III, 52%	with less than 6 months clinical follow up and no response to 3 attempts at telephone contact.	cefazolin. Type III: 1g vancomycin+750mg levofloxacin Penicillin allergy: 2 g aztreonam or 900mg clindamycin. Continued until debridement and "in general" for 24 hours postoperatively.	patient (n=51)	G = N H = P I = N J = N

Quality assessment criteria (see Appendix 3 for further detail: Y = yes; N = no; P = partial; U = unreported): A = Eligibility criteria adequate? B = Sample likely to be representative? C = Participation rate adequate? D = Recruitment prospective? E = Antibiotic intervention clearly described? F = Accepted measure of deep infection? G = Completeness of outcome assessment? H = Relevant prognostic factors reported? I = Relevant confounding factors reported? J = Appropriate measure of variability reported?

Risk of bias in included studies

The key risk of bias in the included studies arises from none of the studies having a control group or randomised allocation to groups to explore the effect of the variable of interest, time of administration of antibiotic prophylaxis. Table 1 provides details of the risk of bias assessment for individual studies (see appendices 2 and 3, supplementary file for details of criteria and results). The majority of studies used consecutive selection or other methods suggesting that the study sample is likely to be representative, though for many of these studies the completeness of outcome data used in the analyses was not considered adequate. The majority of studies reported data on relevant prognostic and confounding variables, though few reported on all the variables we identified in advance as potentially important to consider. Only one study used a robust measure of deep infection based on our pre-defined criterion.[25] A further study applied the Centers for Disease Control and Prevention diagnostic criteria however these were not fully applied: when an implant is present as would be the case in all the fractures in this study, the presence of deep infection cannot be determined until one year post-surgery according to the Centers for Disease Control and Prevention (CDC) criteria.[6] There were limitations in all of the statistical analyses, either in reporting and/or the actual analyses (see Appendices 3 and 4). In addition, only the study by Lack et al. reported a sample size calculation suggesting that the study was adequately powered to determine whether early administration of antibiotics was associated with lower infection rates.[6]

Synthesis of study results

Table 2 provides a summary of the analytical approach, the overall deep infection rate and the results of analyses exploring the relationship between time of antibiotic delivery and deep infection rate for each study. The deep infection rate ranged from 5% to 17.5%, though it is unclear whether this variation is related to characteristics of the participants, setting, the time period of the cohort or variation in the definition of infection used. Four of the studies did not undertake a multivariate analysis, either not planned or insufficient sample size, and therefore other confounding variables were not taken into consideration.[2,23,25,27]

There were limited data available exploring the effect of early administration of antibiotics or delivery in the prehospital setting. Only Thomas et al. explicitly investigated administration of prophylactic antibiotics in the prehospital setting.[2] A further study by Lack et al. used retrospective multivariate analysis to explore the effect of antibiotic delivery within 66 minutes of injury.[6] These two studies were also the most recent cohorts. Lack et al. undertook the most sophisticated analysis, though no information was provided on regression outputs, test statistics or goodness of fit. They reported an independent association between delivery of antibiotic more than 66 minutes after injury (early antibiotics) and the odds of deep infection (Odds Ratio (OR) 3.78; 95% confidence interval (CI) 1.26 to 14.11) in a sample of patients with type III open tibia fractures.[6] There was also an independent association between wound coverage within five days and the risk of infection. The infection rate with early antibiotics and early wound coverage was 2.8% compared to 7.9% for delayed antibiotics and early wound coverage. Thomas et al. reported no statistically significant difference in a composite outcome of fracture site infection or fracture non-union with administration of antibiotic prehospital and on arrival at hospital (risk difference 5.2%, 95% CI -2 to 11%).[2] This difference may be of clinical significance, however, the results cannot be considered robust due to limitations in the analysis.

Weber et al., the largest included study, reported no statistically significant association between developing a deep infection and time of antibiotic administration (adjusted OR 1.0; 95% CI 0.95 to 1.05) in a population with open long bone fractures (66% Gustilo-Anderson Grade I or II).[24] However, this study did not address the effect of prehospital delivery of antibiotics. Based on the IQR only 25% of participants received their antibiotic within 1 hour 40 minutes of injury. In the studies by Dellinger et al., Zumsteg et al. and Leonidou et al. the proportion of patients receiving their antibiotic very early in the prehospital setting was unclear as the cut-off used in the analysis was above and below three hours; none found an effect, though the number of events was low and it is unlikely the studies were sufficiently powered (Table 2).[12,23,25] Al-Aarabi also had a small number of events, the majority of who had received antibiotic within 2 hours of injury.[27]

Table 2 Results from studies on the association between timing of antibiotic and deep infection

| Study | Analysis | Deep infection rate | Summary of results for time to antibiotic delivery and deep infection rate | | |
			Time to antibiotic delivery	% infection rate (n=)	Other information
Al-Arabi[27]	Univariate linear regression	6.8% (n=9)	< 2 hours	9.2% (n=6/65)	
			2-4 hours	2.2% (n=1/45)	
			4-6 hours	0% (n=0/14)	
			6-8 hours	0% (n=0/4)	
			8-12 hours	0% (n=0/3)	
			> 12 hours	100% (n=2/2)	
Dellinger[12]	Univariate analysis followed by stepwise multivariate logistic regression	16% (n=42) (unclear deep or superficial)	≤ 3 hours	16% (n=29/183)	Time to antibiotic delivery not significantly different between fracture related infection and no infection groups (2 hours ± 1.1* c.f. 2.2 hours ± 1.4*; p="not significant"; *not stated whether SD or SE)
			> 3 hours	17% (n=8/47)	
Enninghorst[26]	Univariate analysis and multivariate logistic regression	17% (n=15)			Mean time 1.2 hours (SE 0.3 hours) The authors state there was no statistically difference between infected and non-infected cases in time to antibiotic delivery (further details not provided).
Lack[6]	Receiver operator characteristic (ROC) curves to determine the threshold predictive of infection for continuous variables. Univariate analysis followed by backward stepwise multivariate logistic regression	17.5% (n=24)	< 66 minutes	7% (n=4/57)	Multivariate analysis: Antibiotics delivered > 66 minutes from injury = odds ratio (OR) of infection 3.78 (95% CI 1.26-14.11) Wound coverage > 5 days = OR 7.39 (95% CI 2.54 to 27.04) Immediate antibiotics + early coverage infection rate 2.8%; Delayed antibiotics + early coverage 7.9%; Immediate antibiotics + delayed coverage 14.3%; Delayed antibiotics + delayed coverage 40.5%
			> 66 minutes	25% (n=20/80)	

Study	Statistical test	Infection rate	Time category	Outcome	Result
Leonidou[25]	Fisher's exact test	4.3% (n=7)	≤ 3 hours > 3 hours	4% (n=5/129) 6.3% (n=2/32)	p=0.62
Thomas[2]	Kruskal-Wallis test	Not reported	HEMS group = median 47 minutes (range 27-109, IQR 37-60) Hospital group = median 77 minutes (range 33-189, IQR 65-92)	Composite outcome (fracture site infection or non-union): HEMS group 7.7% (n=1/13) Composite outcome fracture site infection or non-union: Hospital group 12.9% (n=9/70)	Time to delivery significantly different between groups (p=0.001) Risk difference of composite outcome between groups 5.2% (95% CI -2% to 11%)
Weber[24]	Univariate logistic regression and multivariate regression	6% (n=46)	No infection group (n=691): Median = 3.1 hours(IQR 1.7-7.5) Infection group (n=46): Median = 2.6 hours (IQR 1.5-7)		p=0.676 Multivariate regression indicated no significant association between developing a deep infection and time of antibiotic administration (adjusted OR 1.0; 95% CI: 0.95 to 1.05)
Zumsteg[23]	Bivariate logistic regression	5% (n=10)	No infection group (n=190): Mean 2.6 hours (SD 2.2) Infection group (n=10): Mean 1.6 hours (SD 0.9)		None of the analysed factors were significantly associated with deep infection

DISCUSSION

This systematic review identified no randomised or non-randomised controlled studies of the effect of the timing of delivery of antibiotics on the risk of developing deep infection following an open fracture. The eight cohort studies that were identified included 2,142 participants and the reported rate of deep infection ranged from 5 to 17.5%, although the criteria used to define deep infection were not consistent. All of the studies were at risk of bias in multiple areas and there were limitations in the analyses of all of the studies. One study reported an odds ratio of 3.8 (95% CI 1.3-14.1) of an increased risk of deep infection if antibiotics were given more than 66 minutes after the time of injury,[6] however none of the remaining seven studies demonstrated any statistically significant association between the timing of delivery of antibiotics despite the presence of large effect sizes.[2]

There has been no previously published systematic review on this subject. A previous systematic review found that the delivery of antibiotics protected against early infection compared to no antibiotics or placebo in the treatment of open fractures of the lower limb.[35] The effect of the timing of delivery of antibiotics was excluded from that review. Whilst there has been recently published evidence to suggest a reduced rate of deep infection in severe (grade 3) open fractures of the lower limb,[6] the lack of a control group in this study, the non-standard application of the CDC criteria to diagnose deep infection and the retrospective restriction to confirmed grade 3 open fractures substantially limits the generalizability of the findings. The remaining identified studies suggest there may be a substantial effect size according to the timing of antibiotic delivery[2] but no statistically significant differences were demonstrated.[2,12,23-27]

The strengths and potential limitations of this systematic review deserve consideration. This is a comprehensive and up to date systematic review of the literature available to date in this area. The review was conducted in accordance with the PRISMA guidelines and registered prospectively in the PROSPERO database (CRD42015016729). The risk of bias and quality assessment were assessed and checked by a second author for all identified studies.

The conclusions of this systematic review are limited by the quality of the evidence available in the literature for review. There were no controlled trials on the effect of the timing of delivery of antibiotics on the risk of deep infection following open fracture and all of the included studies are therefore at risk of substantial bias. Along with the methodological issues, such as the lack of consistency in the definition of deep infection, evaluation of different grades of open fractures and limitations of the analyses identified in the included studies, our ability to reach a firm conclusion regarding the effect of the intervention in this population was limited. As such, the conduct of a randomised controlled trial to assess the effect of this intervention is indicated.

There is not currently sufficiently robust evidence available to determine whether the timing of delivery of intravenous antibiotics has an effect on the risk of deep infection, patient reported outcome or health related quality of life following open limb fractures. Further there is no current robust evidence base to support the routine prehospital delivery of antibiotics compared to delivery in hospital for patients with an open fracture of the lower limb. Before the policy and guidance can be changed to support the use of prehospital antibiotics in this population, a randomised controlled trial should be performed to determine whether there is a benefit in terms of patient outcome that justifies the resource implications of widespread introduction of this practice.

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