BJR

INFECTION

The effect of local antibiotic prophylaxis when treating open limb fractures

A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objectives

As well as debridement and irrigation, soft-tissue coverage, and osseous stabilization, systemic antibiotic prophylaxis is considered the benchmark in the management of open fractures and considerably reduces the risk of subsequent fracture-related infections (FRI). The direct application of antibiotics in the surgical field (local antibiotics) has been used for decades as additional prophylaxis in open fractures, although definitive evidence confirming a beneficial effect is scarce. The purpose of the present study was to review the clinical evidence regarding the effect of prophylactic application of local antibiotics in open limb fractures.

Methods

A comprehensive literature search was performed in PubMed, Web of Science, and Embase. Cohort studies investigating the effect of additional local antibiotic prophylaxis compared with systemic prophylaxis alone in the management of open fractures were included and the data were pooled in a meta-analysis.

Results

In total, eight studies which included 2738 patients were eligible for quantitative synthesis. The effect of antibiotic-loaded poly(methyl methacrylate) beads was investigated by six of these studies, and two studies evaluated the effect of local antibiotics applied without a carrier. Meta-analysis showed a significantly lower infection rate when local antibiotics were applied (4.6%; 91/1986) than in the control group receiving standard systemic prophylaxis alone (16.5%; 124/752) ($p < 0.001$) (odds ratio 0.30; 95% confidence interval 0.22 to 0.40).

Conclusion

This meta-analysis suggests a risk reduction in FRI of 11.9% if additional local antibiotics are given prophylactically for open limb fractures. However, due to limited quality, heterogeneity, and considerable risk of bias, the pooling of data from primary studies has to be interpreted with caution.

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Article focus

- Local antibiotics have been used for decades as prophylaxis in open fractures, but the evidence for its beneficial effect is scarce.
- The purpose of the present study was to review the evidence regarding the effect of prophylactic application of local antibiotics in open limb fractures and to identify clinically available applications and carriers for local antibiotics.

Key messages

- This meta-analysis suggests a considerable risk reduction if additional local antibiotics are applied in open limb fractures.
- Primary studies investigating the prophylactic effect of absorbable carriers including implant coatings for local antibiotic delivery show promising results.

Strengths and limitations

- Systematic review of currently available literature including eight comparative studies and ten case series.
- Due to limited quality, heterogeneity, and considerable risk of bias, the pooling of data from primary studies has to be interpreted with caution.

Introduction

Open limb fractures are often associated with considerable bone damage, including periosteal stripping, extensive soft-tissue trauma, and severe contamination.[1,2] This enables bacteria to breach the damaged skin barrier and to adhere to non-living surfaces, such as implants or dead bone fragments, and to establish a fracture-related infection (FRI).[3] After attachment, the bacteria grow in biofilms that protect the pathogens from antibiotics and host immune defences. Biofilm formation is one of the major reasons that FRI is very challenging to treat.[1,3,4] FRIs may occur in up to 30% of complex open fractures and are associated with a significant socioeconomic impact,[5,6] and so a principal objective in the management of open fractures is to prevent infection.[7]

As well as debridement and irrigation, soft-tissue coverage, and osseous stabilization, systemic antibiotic prophylaxis is the benchmark in the management of open fractures and has been shown to considerably reduce the risk of subsequent FRI.[8-10]

However, the local vascular anatomy is often disrupted in complex open limb fractures, leading to reduced tissue concentrations of systemically administered antibiotics. Locally administered antibiotics may overcome this issue with the antibiotic delivered directly to the surgical site, with the resultant tissue concentrations being many times higher than those achieved after systemic antibiotic administration.[11] In addition, high local antibiotic levels can be achieved even when local vasculature is compromised and the risk of toxic systemic levels is avoided.[11,12] Locally administered antibiotics may also prevent bacteria from colonizing any implant or non-viable tissue surfaces and prevent biofilm formation.[6]

Although local antibiotics have been used prophylactically for many years in open limb fractures, the available evidence for its beneficial effect is limited.[13-20]

The purpose of the present study was to review the current literature for evidence regarding the effect of prophylactic application of local antibiotics in open limb fractures. The secondary aim was to identify clinically available applications and carriers for local antibiotics.

Materials and Methods

Reporting guidelines. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the Meta-analyses of Observational Studies in Epidemiology guidelines, and the Cochrane Handbook for Systematic Reviews of Interventions were followed.[21-23] The review was prepared and maintained using the software programme RevMan5 (Version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology was used to rate the quality of evidence.[24]

Data sources and search strategy. The search was performed with the help of a biomedical information specialist in the PubMed, Web of Science, and Embase databases, and was limited to studies published up to 1 August 2017. The main three search concepts were open fractures, antibiotic prophylaxis, and infection (supplementary material).

Eligibility and study selection. After all the publications had been identified, duplicates were removed and study selection was accomplished by two independent reviewers (MM and AV) in three phases. Disagreements were resolved through discussion with a third reviewer (WJM).

A PRISMA flow diagram provides an overview of the selection process and the number of papers retrieved and excluded, together with reasons, at various stages (Fig. 1).

Studies were assessed for eligibility against the following criteria[25]: 1) population – patients with an open long-bone fracture; 2) intervention – supplementary locally delivered antibiotics at open fracture site; 3) comparator – prophylactic intravenous antibiotics only; 4) outcome – infection at former fracture site occurring in the follow-up period[3] (due to the absence of a dedicated definition for FRI until recently,[26-28] details on the definition of FRI were also recorded); and 5) study design. The following study designs were included: randomized controlled trials (RCTs) and prospective and retrospective observational designs investigating the effectiveness of supplemental local antibiotics *versus* systemic antibiotic prophylaxis alone in open limb fractures.

Studies restricted to the following populations or interventions were excluded: paediatric patients; local or systemic antibiotics in treatment of established infections; open fractures associated with previous ulcers or with HIV/AIDS; open fractures not involving long bones; open fractures in the context of military conflicts or associated with gunshots or explosions; experimental studies or animal studies; and studies written in any language other than English.

Data extraction. Extracted data from the eligible papers were entered into RevMan5 (Version 5.3) and are summarized in Table I and in the supplementary material. Comparative studies directly comparing locally delivered antibiotics with standard systemic prophylaxis were considered for quantitative synthesis in a meta-analysis. Observational case series evaluating the effect of local antibiotics, but lacking a control group, were summarized in a qualitative analysis and narrative review.

Assessment of the bias and confidence in the effect. In both RCTs and non-RCTs, the GRADE methodology was used independently by two reviewers to rate the quality of evidence in one of the four categories of evidence: high, moderate, low, and very low.[24]

Data synthesis and statistical analysis. The data from primary studies comparing the effect of local antibiotics against systemic antibiotics alone on the risk of

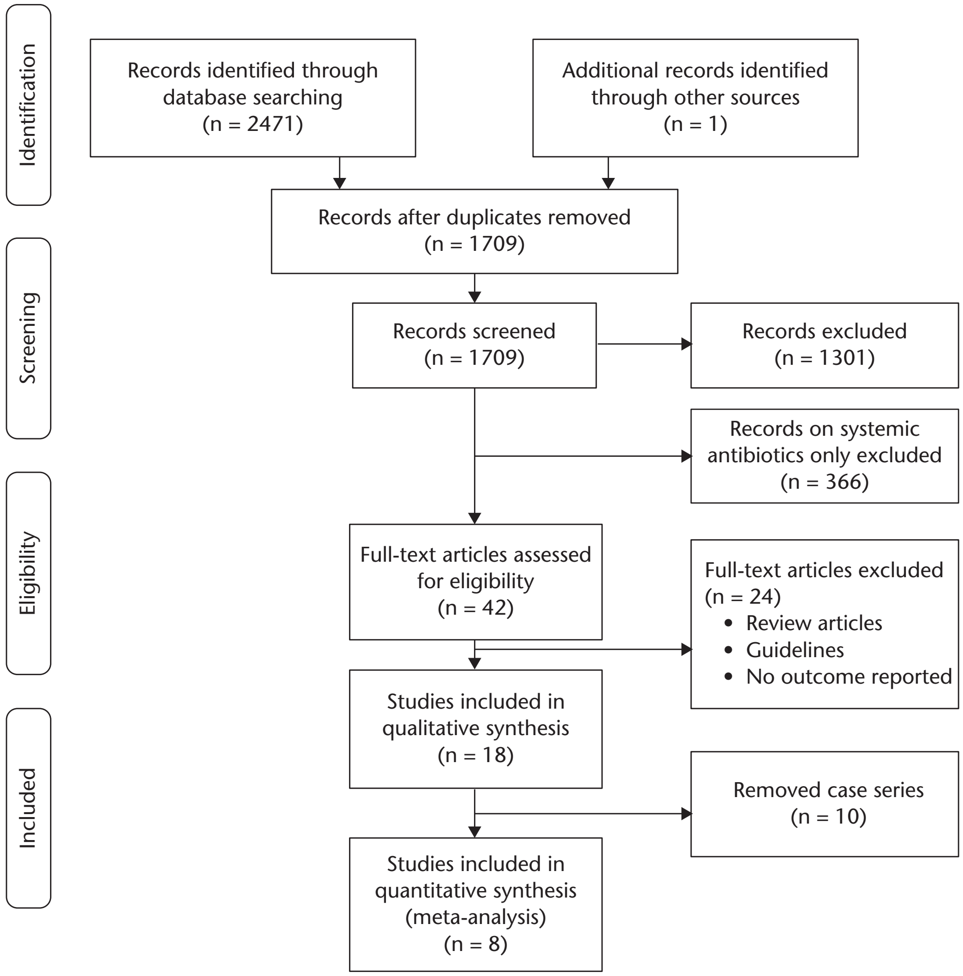

Fig. 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram: eligibility assessment.

a subsequent FRI was pooled in a meta-analysis. The pooled odds ratio (OR) for dichotomous outcome measures with the associated 95% confidence interval (CI) was calculated for infection using a fixed-effect model applying the Mantel-Haenszel method.[21]

The statistical heterogeneity was assessed using a chi-squared test. The I^2 statistic was used to quantify the heterogeneity of included studies by quantifying the proportion of the variation in point estimates due to differences between the studies.[21,29] Calculations were performed in RevMan5.

Results

Following screening and confirmation of eligibility, 18 articles were available for analysis. Further review of these studies revealed the absence of a control group in ten case series, leaving eight studies eligible for quantitative analysis (Fig. 1). One of these records was identified through other sources, namely in the systematic review of Craig et al.[6,20]

Overview of selected studies for quantitative analysis. Table I provides an overview of the primary studies included for quantitative analysis (supplementary material): one RCT[17] and seven retrospective case-control studies,[13-16,18-20] with a total of 2738 analyzed open fractures.

FRI was the primary outcome of interest in all of the included studies. However, there was considerable variation in the definition of FRI, if in fact it was defined at all (Table I).

The mean follow-up period was reported in only four studies and ranged from 11 to 23 months.[13,16,17,19]

The majority of the studies (six studies) investigated the prophylactic effect of tobramycin-loaded poly(methyl methacrylate) (PMMA) beads placed in the open fracture wound.[13-17,20] The remaining two studies investigated the effect of local antibiotics that were applied without a carrier in the fracture wound: vancomycin powder[18] and aqueous aminoglycosides.[19]

Quality assessment of included studies for quantitative analysis. The quality of the evidence ranged from very low to moderate (Table I). The quality of the single RCT included was rated moderate due to a risk of bias because of the lack of reporting of prognostic factors, non-consecutive enrolment, and missing robust

Table I. Characteristics of eligible studies for quantitative analysis

Study/characteristic	Details
01_Henry et al[13] (1990)	
Study title	The role of local antibiotic therapy in the management of compound fractures
Objective	Effect of tobramycin PMMA beads in open fracture wounds for temporary wound coverage
Setting	Single centre in the United States (Humana Hospital, University of Louisville)
Level of evidence	Low
Study design	Retrospective cohort study
Selection of participants	Consecutive
Follow-up interval	Control group: 20.9 mths (6 to 50); intervention group: 17.5 mths (6 to 51)
Inclusion criteria	Open limb fractures
Number of open fractures for analysis	404
Gustilo–Anderson	I: 127 (31%); II: 153 (39%); III: 124 (31%)
Report of relevant prognostic factors	Partially
Systemic antibiotics in both groups	Yes, penicillin, cefazolin, tobramycin
Intervention group: local antibiotics	Tobramycin PMMA beads
Matching of cohorts	Yes
Outcome parameter(s)	Wound infection and/or bone infection
Definition of infection?	Incomplete; infection = identification of pathogen in culture
02_Ostermann et al[14] (1993)	
Study title	The role of local antibiotic therapy in the management of compound fractures
Objective	Effect of tobramycin PMMA beads in open fracture wounds for temporary wound coverage
Setting	Single centre in the United States (University of Louisville)
Level of evidence	Low
Study design	Retrospective cohort study
Selection of participants	Consecutive
Follow-up interval	Not reported
Inclusion criteria	Open limb fractures
Number of open fractures for analysis	704
Gustilo–Anderson	I: 198 (28%); II: 259 (37%); III: 247 (35%)
Report of relevant prognostic factors	Partially
Systemic antibiotics in both groups	Yes, penicillin, cefazolin, tobramycin
Intervention group: local antibiotics	Tobramycin PMMA beads
Matching of cohorts	Similar case-matching reported: grade open fracture, age, gender, fracture location, follow-up interval; no matching in wound closure
Outcome parameter(s)	Wound infection and/or bone infection
Definition of infection?	Incomplete; infection = identification of pathogen in culture; bone infection = “deep bony infection occurring after 6 weeks”
03_Ostermann et al[15] (1995)	
Study title	Local antibiotic therapy for severe open fractures. A review of 1085 consecutive cases
Objective	Effect of tobramycin PMMA beads in open fracture wounds for temporary wound coverage
Setting	Single centre in the United States (University of Louisville)
Level of evidence	Low
Study design	Retrospective cohort study
Selection of participants	Consecutive
Follow-up interval	Not reported
Inclusion criteria	Open limb fractures
Number of open fractures for analysis	1085
Gustilo–Anderson	I: 279 (26%); II: 364 (34%); III: 442 (41%)
Report of relevant prognostic factors	Partially
Systemic antibiotics in both groups	Yes, penicillin, cefazolin, tobramycin
Intervention group: local antibiotics	Tobramycin PMMA beads
Matching of cohorts	Similar case-matching reported: grade open fracture, age, gender, fracture location, follow-up interval; no matching in wound closure
Outcome parameter(s)	Wound infection and/or bone infection
Definition of infection?	Not reported
04_Keating et al[16] (1996)	
Study title	Reamed nailing of open tibial fractures: does the antibiotic bead pouch reduce the deep infection rate?
Objective	Determine whether addition of the bead pouch to a standard protocol of wound management of open fractures was associated with a concomitant reduction in the rate of deep infection
Setting	Single centre in the United Kingdom
Level of evidence	Low
Study design	Retrospective cohort study
Selection of participants	Consecutive: first control (historical group), then intervention group
Follow-up interval	23 mths (12 to 50)
Inclusion criteria	Grade II and III open tibial fractures
Number of open fractures for analysis	78

(Continued)

Table I. (Continued)

Study/characteristic	Details
Gustilo–Anderson	II: 38 (49%); III: 40 (51%)
Report of relevant prognostic factors	Partially
Systemic antibiotics in both groups	For 72 hrs: cefazolin every 8 hrs; grade III fracture: additional gentamicin
Intervention group: local antibiotics	Tobramycin PMMA beads
Matching of cohorts	Similar case-matching reported: fracture comminution, age, gender, mean time to wound coverage
Outcome parameter(s)	Deep infection and/or nonunion
Definition of infection?	Incomplete: “presence of a purulent discharge, with bony involvement evident at the time of surgical debridement”
05_Moehring et al[17] (2000)	
Study title	Comparison of antibiotic beads and intravenous antibiotics in open fractures
Objective	Efficacy of antibiotic-impregnated beads compared with conventional intravenous antibiotics in the treatment of open fractures
Setting	Single centre in the United States (University of California)
Level of evidence	Moderate
Study design	Randomized prospective study
Selection of participants	Consecutive enrolment not possible because patients declined to consent or inadvertently were omitted
Follow-up interval	15 mths (12 to 27)
Inclusion criteria	Grade II and IIIA/B open long-bone fracture
Number of open fractures for analysis	62
Gustilo–Anderson	Not reported
Report of relevant prognostic factors	No
Systemic antibiotics in both groups	Cefazolin + aminoglycoside or anaerobic coverage or both added for Grade IIIA/B fractures
Intervention group: local antibiotics	Tobramycin PMMA beads; no further systemic antibiotics
Control group: additional antibiotics	Yes, intravenous cephalosporin and gentamicin until wound coverage
Matching of cohorts	Similar case-matching reported: fracture comminution, age, gender, time to wound coverage
Outcome parameter(s)	Infection
Definition of infection?	Incomplete: “Persistent drainage, that was positive on culture, from an open fracture site or wound that had broken down”
Further information	A third group of 13 fractures was not randomized and received both local and systemic antibiotics (due to limb saving or other reasons). This group was not taken into consideration for this meta-analysis.
06_Ziran et al[20] (2004)	
Study title	Intramedullary nailing in open tibial fractures: a comparison of two techniques
Objective	Comparison of reamed and unreamed tibial nailing in terms of union and infection rate; subgroup analysis: effect of antibiotic beads in IIIB open tibial fractures
Setting	United States, not reported if single or multicentre trial
Level of evidence	Very low
Study design	Retrospective cohort study
Selection of participants	Consecutive
Follow-up interval	Not reported
Inclusion criteria	Grade IIIB open tibial fractures for subgroup analysis
Number of open fractures for analysis	28
Gustilo–Anderson	III: 28 (100%)
Report of relevant prognostic factors	No
Systemic antibiotics in both groups	Penicillin, cefazolin, and gentamicin
Intervention group: local antibiotics	Tobramycin PMMA beads
Matching of cohorts	Similar case-matching for all 51 fractures stated but no detailed information given
Outcome parameter(s)	Infection
Definition of infection?	None
Further information	In total, 51 open tibial fractures investigated: 22 reamed and 29 unreamed. In reamed IIIB open tibial fractures, PMMA beads were applied to wound. Just 28 IIIB open tibial fractures are considered in this systematic review. Level of evidence rated very low because prophylactic effect of local antibiotics in open fractures was investigated in just a small cohort.
07_Singh et al[18] (2015)	
Study title	Surgical site infection in high-energy periarticular tibial fractures with intra-wound vancomycin powder: a retrospective pilot study
Objective	Assess the efficacy of intraoperative vancomycin powder administration on preventing deep surgical site infection
Setting	Single centre in the United States (Vanderbilt Orthopaedic Institute)
Level of evidence	Very low
Study design	Retrospective cohort study
Selection of participants	Consecutive
Follow-up interval	Average not reported (minimum 6 mths)
Inclusion criteria	Articular tibial fractures, adult, staged fixation with > 5 days after injury
Number of open fractures for analysis	26
Gustilo–Anderson	Not reported
Report of relevant prognostic factors	Partially
Systemic antibiotics in both groups	Cefazolin every 8 hrs for 24 hrs

(Continued)

Table I. (Continued)

Study/characteristic	Details
Intervention group: local antibiotics	1 g vancomycin powder into surgical wound at time of definitive fixation
Matching of cohorts	Similar case-matching for age, gender, smoking, diabetes, fracture location (of all 93 cases)
Outcome parameter(s)	Deep surgical site infection
Definition of infection?	Surgical site infection not specified
Further information	In total, 93 tibial fractures analyzed. For this review, only the 26 open fractures were taken into account. Level of evidence rated very low because prophylactic effect of local antibiotics in open fractures was investigated in just a small cohort.
08_Lawing et al[19] (2015)	
Study title	Local injection of aminoglycosides for prophylaxis against infection in open fractures
Objective	Determine efficacy of local aminoglycosides (gentamicin and tobramycin), in conjunction with systemic antibiotics, to lower the prevalence of infection in patients with open fractures
Setting	Single centre in the United States (University of North Carolina)
Level of evidence	Moderate
Study design	Retrospective cohort study
Selection of participants	Consecutive
Follow-up interval	Control group: 12.5 mths; intervention group: 11.3 mths
Inclusion criteria	Open fractures
Number of open fractures for analysis	351
Gustilo–Anderson	I: 44 (12%); II: 139 (40%); III: 168 (48%)
Report of relevant prognostic factors	Yes (very detailed)
Systemic antibiotics in both groups	Cefazolin; in grade III fractures gentamicin added; in contaminated fractures penicillin added
Intervention group: local antibiotics	Local aminoglycoside injection after wound closure
Matching of cohorts	Similar case-matching for age, gender, polytrauma; multivariate analysis was performed to adjust for potential differences for confounding variables
Outcome parameter(s)	Infection
Definition of infection?	CDC definition of superficial and deep infection

PMMA, poly(methyl methacrylate); CDC, Centers for Disease Control and Prevention

measures for infection.[17] In contrast, in their cohort study, Lawing et al[19] used an established definition for infection, reported detailed relevant prognostic factors, and performed a multivariate analysis to adjust potential differences for confounding variables. The GRADE approach was performed in accordance with the published criteria.[24]

All included observational studies used a consecutive enrolment, suggesting that the reported study population is likely to be representative. Most of the studies reported some relevant prognostic factors and case-matching,[13-16,18,19] whereas only one study covered several important confounding variables and used them for a multivariate analysis.[19]

Seven studies have a substantial risk of bias, mainly due to the lack of a robust definition of the primary outcome parameter infection. None of the studies reported a sample size calculation.

The I^2 statistic for the included studies was 21%, suggesting that there was low statistical heterogeneity (Fig. 2).[30] However, there was considerable clinical heterogeneity among the included studies, which was due to differing patient populations (e.g. Gustilo–Anderson grade and fracture localizations), interventions, outcome measures, follow-up intervals, and study designs (Table I).

Merging all considerations in the GRADE process, the body of evidence of all studies was rated low. Since the two very low-ranked studies are of small sample size and are contributing only 2.0% of all fractures (54 out of 2738 fractures) to the meta-analysis, the overall body of evidence was rated low rather than very low.

Synthesis of study results. The effect of additional local antibiotics *versus* systemic antibiotic prophylaxis on subsequent infection was analyzed for every individual study and across all studies in a meta-analysis, and results are summarized in Table II and Figure 2. The overall infection rate of all 2738 reported fractures was 7.9% (n = 215).

Results from the meta-analysis suggest a large reduction in infection risk with the use of additional local antibiotics (OR = 0.30; 95% CI 0.22 to 0.40). Open fractures that received local antibiotic prophylaxis subsequently had an infection rate of 4.6%, whereas open fractures treated with standard systemic prophylaxis alone had an infection rate of 16.5% ($p < 0.001$).

Local antibiotics were associated with a lower infection rate compared with the control group in all three Gustilo–Anderson grades (Table III).

Results from qualitative analysis. A qualitative analysis was performed in the ten studies that were excluded from the meta-analysis for a lack of control group (supplementary material).[30-39] Five of these studies investigated the effect of PMMA containing tobramycin[31,32,39] or the combination of tobramycin and vancomycin, and reported an infection rate from 0% to 20.0%.[33,35] Chaudhary et al[37] assessed the efficacy of gentamicin-impregnated collagen fleeces in the treatment of open fractures and found an infection rate of 16.1%. Cai et al[36] observed no infection in 26 open long-bone fractures treated with

Study or subgroup	Local antibiotics Events	Local antibiotics Total	Systemic antibiotics Events	Systemic antibiotics Total	Weight	Odds ratio M-H, Fixed, 95% CI
01_Henry et al[13] (1990)	14	334	15	70	16.0%	0.16 [0.07, 0.35]
02_Ostermann et al[14] (1993)	23	547	26	157	26.1%	0.22 [0.12, 0.40]
03_Ostermann et al[15] (1995)	31	845	29	240	29.3%	0.28 [0.16, 0.47]
04_Kaeting et al[16] (1996)	2	53	4	25	3.5%	0.21 [0.04, 1.21]
05_Moehring et al[17] (2000)	2	24	2	38	1.0%	1.64 [0.21, 12.47]
06_Ziran et al[20] (2004)	2	12	5	16	2.4%	0.44 [0.07, 2.80]
07_Singh et al[18] (2015)	1	3	7	23	0.7%	1.14 [0.09, 14.78]
08_Lawing et al[19] (2015)	16	168	36	183	21.0%	0.43 [0.23, 0.81]
Total (95% CI)		**1986**		**752**	**100.0%**	**0.30 [0.22, 0.40]**
Total events	91		124			

Heterogeneity. $Chi^2 = 8.83$, $df = 7$ $(P = 0.27)$; $I^2 = 21\%$

Test for overall effect: $Z = 7.97$ $(P < 0.00001)$

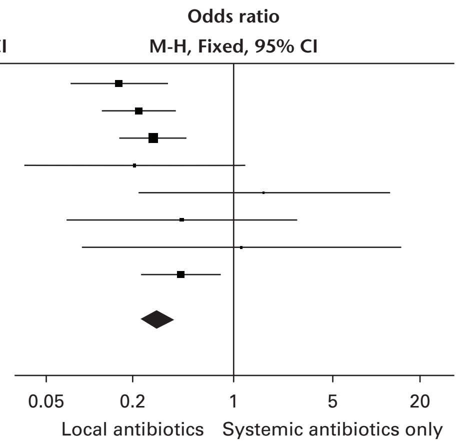

Fig. 2

Forest plot presenting fracture-related infection with additional local antibiotics *versus* systemic antibiotic prophylaxis alone in open limb fractures. Blue squares represent the odds ratio (OR), whereas values < 1.0 indicate that the addition of local antibiotics is associated with decreased risk of infection. The vertical line (OR = 1) indicates no effect of local antibiotics. A value of > 1.0 indicates an increased risk of infection if additional local antibiotics were given. Horizontal lines represent the 95% confidence intervals (CIs), whereas lines that do not cross 1.0 indicate significant difference. The diamond is demonstrating the meta-analysis: horizontal tips equal the CI, vertical tips equal the pooled OR (Mantel–Haenszel (M–H)).

Table II. Quantitative analysis of primary studies: number of fractures, number of infections, and infection rate in all reported open fractures, in the intervention group, and in the control group; 13 patients who were not randomized and received local antibiotics are not included in this analysis

Study (year)	All open fractures			Intervention group (additional local antibiotics)			Control group (systemic antibiotics only)			p–value*
	Fractures, n	Infections, n	Infection rate, %	Fractures, n	Infections, n	Infection rate, %	Fractures, n	Infections, n	Infection rate, %	
01_Henry et al[13] (1990)	404	29	*7.2*	334	14	*4.2*	70	15	*21.4*	< 0.001
02_Ostermann et al[14] (1993)	704	49	*7.0*	547	23	*4.2*	157	26	*16.6*	< 0.001
03_Ostermann et al[15] (1995)	1085	60	*5.5*	845	31	*3.7*	240	29	*12.1*	< 0.001
04_Keating et al[16] (1996)	78	6	*7.7*	53	2	*3.8*	25	4	*16.0*	0.079
05_Moehring et al[17] (2000)	62	4	*6.5*	24	2	*8.3*	38	2	*5.3*	0.637
06_Ziran et al[20] (2004)	28	7	*25.0*	12	2	*16.7*	16	5	*31.3*	0.662
07_Singh et al[18] (2015)	26	8	*30.8*	3	1	*33.3*	23	7	*30.4*	1
08_Lawing et al[19] (2015)	351	52	*14.8*	168	16	*9.5*	183	36	*19.7*	0.010
Overall	2738	215	*7.9*	1986	91	*4.6*	752	124	*16.5*	< 0.001

*Fisher's exact test

local vancomycin-loaded calcium-sulphate pellets. Three series reported no deep infection after treating; in total, 22 open tibial fractures with a polylactic acid/gentamicin-coated tibial nail.[30,34,38]

Discussion

This systematic review identified one RCT and seven cohort studies investigating the prophylactic effect of local antibiotics on the risk of developing a FRI following open fracture. The pooled meta-analysis, enrolling a total of 2738 open limb fractures, suggested a large beneficial effect of locally applied antimicrobials, when compared with systemic prophylaxis only. This effect was present in all three main Gustilo–Anderson grades.

However, these results should be interpreted with caution due to the low rating of the recommendation when evaluated using the GRADE approach and, therefore, the uncertain impact of heterogeneity and bias on the pooled data results.[40]

The clinical heterogeneity is mainly due to different patient populations, fracture localizations, study designs, interventions, follow-up intervals, and definitions of infection.

Only one study in this review used an established definition for infection, namely the Centers for Disease Control and Prevention guidelines for surgical site infections (SSI). However, this definition was not exclusively designed for FRIs and has considerable limitations when applied to patients with fractures.[19,27,41,42] Incomplete and imprecise definitions of infection were provided in four studies,[13,14,16,17] with three studies providing no description of their primary outcome.[15,18,20] An international consensus

Table III. Infection rates divided by Gustilo–Anderson (GA) grade between systemic and local antibiotics

GA grade	All open fractures*			Intervention group (additional local antibiotics)			Control group (systemic antibiotics only)			OR (95% CI)	p-value
	Fractures, n	Infections, n	Infection rate, %	Fractures, n	Infections, n	Infection rate, %	Fractures, n	Infections, n	Infection rate, %		
I	604	9	*1.5*	471	3	*0.6*	133	6	*4.5*	0.14 (0.03 to 0.55)	0.005
II	814	39	*4.8*	643	20	*3.1*	171	19	*11.1*	0.26 (0.13 to 0.49)	< 0.001
III†	1085	103	*12.4*	677	49	*7.2*	204	54	*26.5*	0.22 (0.14 to 0.33)	< 0.001
All	2299	151	*6.8*	1791	72	*4.0*	508	79	*15.6*	0.22 (0.16 to 0.31)	< 0.001

*Three primary studies (including 439 fractures) do not provide detailed information on GA grade[17-19]
†Subgrouping of Gustilo–Anderson grade III fractures in A, B and C not possible due to missing information in primary studies
GA, Gustilo–Anderson; OR, odds ratio; CI, confidence interval

group meeting has recently proposed a standardized definition of FRI in response to a systematic review, which found that only 2% of fracture management trials provided a recognized definition of infection.[26,27]

Another important factor of clinical heterogeneity is that five primary studies used different anatomical locations[13-15,17,19] and only three studies focused solely on tibial fractures.[16,18,20] Rates of FRI vary significantly between different anatomical locations,[43] and grouping open fractures of upper and lower extremity together in one analysis introduces a degree of bias. A subgroup analysis of one anatomical location would be desirable, but with a low number of cases it is difficult to produce a meaningful conclusion.

The large-scale studies of Henry et al[13] and Ostermann et al[14,15] found a beneficial effect of locally applied tobramycin PMMA beads. This finding was supported by Keating et al,[16] who reported a trend towards reduced risk of FRI with the addition of local tobramycin-loaded PMMA beads (Table II and Fig. 2).

Conversely, the only RCT in this meta-analysis did not find any beneficial effect in preventing FRI with the use of tobramycin-loaded PMMA beads. Moehring et al[17] reported an increased risk of FRI with the use of antibiotic-loaded PMMA depots (8.3% *vs* 5.3%). However, this study is associated with a considerable risk of bias due to patient prognostic factors not being reported, inadequate case-matching with regard to Gustilo–Anderson grade, and the absence of a clearly defined primary outcome (Table I). The somewhat greater infection rate in the intervention group may be explained by the smaller group size and by the fact that this cohort received just a single-dose systemic antimicrobial prophylaxis, whereas in the control group, systemic antibiotics were continued until wound coverage.[17] Although antibiotic beads alone can provide high antimicrobial levels at the fracture site, their effects may be limited beyond the fracture site.

Ziran et al[20] also investigated the effect of tobramycin-loaded PMMA beads and reported a twofold risk reduction in infection rate (31.3% *vs* 16.7%). However, due to the small sample size, the study is associated with a considerable risk of bias and the results should be interpreted with caution.

PMMA has been in use since the 1970s and is the most widely studied carrier in this review. Due to its beneficial effect, antibiotic-impregnated PMMA beads should not be neglected in the acute management of open fractures and offer a treatment option for cases that need a planned second-look operation. PMMA is non-biodegradable and, therefore, requires surgical removal, which limits its application after definitive wound closure. In addition, following the initial high level of antibiotic released from PMMA, there is a prolonged low-level antibiotic release that may be below the minimum inhibitory concentration for potential pathogenic organisms, resulting in a selection pressure that favours the emergence of resistant strains, as well as potentially inciting a foreign body reaction.[11]

There were two studies included in this review that investigated the effect of local antibiotics without a carrier.[18,19] The main advantage of this technique is that the antimicrobial can be applied at wound closure and does not require surgical removal. A previous meta-analysis with a limited quality of evidence showed a significant protective effect of topical vancomycin powder in reducing SSI rate in spinal surgery.[44] Owen et al[45] reported in a recently published cohort study a significant reduction of postoperative infection if vancomycin or tobramycin powder were applied in pelvic/acetabular fracture surgery. In open articular tibial fractures, Singh et al[18] found no beneficial effect of topical vancomycin, although this study is associated with a considerable risk of bias due to a small sample size and inadequate reporting of soft-tissue involvement and length of follow-up.

O'Toole et al[46] recognized the missing evidence of topical vancomycin in limb fractures and recently published a study outline of a planned multicentre RCT investigating its effect on FRI. The advantages of topical vancomycin are: widespread availability; low cost; efficacy against most common pathogens; and limited concerns regarding inhibition of bone healing or osteogenic cytotoxicity.[46] Nonetheless, there are concerns that in the age of widespread antimicrobial resistance, vancomycin should be reserved for therapeutic, rather than prophylactic, purposes.[19] Lawing et al[19] recognized this and investigated the effect of locally injected aqueous aminoglycosides in open fractures in a methodologically well-designed observational trial. They found a significantly reduced infection rate (9.5%) compared with the control group (19.7%). There was no obvious evidence that local aminoglycosides were inhibiting bone healing since they were not associated with a higher nonunion rate ($p = 0.881$).[19]

The main disadvantage of locally administered antibiotics without a carrier is that there is no controlled delivery of antibiotics directly into target tissues and no sustained release over time.[11] Biodegradable carriers overcome this issue and do not have the limitations of PMMA. New absorbable biocomposites, such as a gentamicin-loaded calcium-sulphate/hydroxyapatite, have been shown to be highly effective in the treatment of chronic osteomyelitis.[47] Malizos et al[48] demonstrated in a recently published multicentre RCT that a fast-resorbable antibiotic-loaded hydrogel significantly reduced infection rates after internal fixation of closed fractures. However, evidence of the effectiveness of degradable carriers in open fractures is limited. Our literature search identified only five case series analyzing the effect of biodegradable antibiotic carriers in open fractures. Even though these studies are associated with a considerable risk of bias, the results are promising. No infections were reported in 26 open fractures treated with vancomycin-loaded calcium-sulphate pellets,[36] nor in 22 open tibial fractures stabilized with a gentamicin-coated tibial nail.[30,34,38]

Our current systematic review provides an update on local antibiotic prophylaxis in open long-bone fractures, including various new absorbable carriers.[11,48,49] The beneficial effect of local antibiotics in open limb fractures was proven by pooling data exclusively from cohort studies that were directly comparing the effect of additional local antibiotics with that of standard systemic antibiotic prophylaxis. The main limitation of this review and meta-analysis is the low quality of evidence available in the literature. Further controlled trials of sufficient statistical power and bias limiting methodologies are required to corroborate the findings of this meta-analysis. Of critical importance is the reporting of trials in accordance with agreed minimum data sets, and the use of a standardized definition of FRI.

Another limitation of this systematic review may be that Henry et al[13] and Ostermann et al[14,15] might have used a cumulative cohort since the same group of authors, from the same centre, using a similar technique, described their results in three different studies. However, since they did not mention having used the same cohort of patients, all three studies were included in this meta-analysis. Assuming a cumulative cohort was used, and excluding their first two studies (Henry et al[13] and Ostermann et al[14]) from our meta-analysis, the recalculation of pooled data would show similar results with a significant risk reduction if local antibiotics were given prophylactically (4.9%) compared with the control group receiving standard systemic prophylaxis alone (15.8%) ($p < 0.001$).

In conclusion, this meta-analysis found a risk reduction (11.9%) of FRI associated with the application of local antibiotics in open limb fractures. However, due to limited quality, heterogeneity, and considerable risk of bias, the pooling of data from primary studies has to be interpreted with caution.

Supplementary material

The search strategy, a detailed data form of primary studies eligible for quantitative analysis, and a table showing the characteristics of eligible studies for qualitative analysis.

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- M. Morgenstern: Principal investigator, Study design, Literature search, Selection process of primary studies, Statistical analysis, Writing the manuscript.
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- M. A. McNally: Assisting in carrying out the study, Reviewing the manuscript.
- T. F. Moriarty: Assisting study design, Assisting in carrying out the study, Reviewing the manuscript.
- J. Y. Ferguson: Assisting in carrying out the study, Reviewing the manuscript.
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- WJ. Metsemakers: Study design, Literature search, Selection process of primary studies, Writing the manuscript.

Conflict of Interest Statement

- None declared