

Supplementary data

Full searches

PubMed (194 hits)

(“Cephalosporins”[Mesh] OR cephalospor*[tiab] OR kefzol[tiab] OR cefazolin[tiab] OR cephazolin[tiab] OR cefamandole[tiab] OR cefuroxime[tiab] OR duricef[tiab] OR keflex[tiab] OR Cefadroxil[tiab] OR velosef[tiab] OR biocef[tiab] OR panixine[tiab] OR cephalixin[tiab] OR ancef[tiab] OR cephradine[tiab] OR ultracef[tiab]) AND (“Lower Extremity”[Mesh] OR “Upper Extremity”[Mesh] OR “Podiatry”[Mesh] OR “Ankle Fractures”[Mesh] OR “Bones of Lower Extremity”[Mesh] OR “Bones of Upper Extremity”[Mesh] OR “Joints”[Mesh] OR orthopedic*[tiab] OR orthopaedic*[tiab] OR joint*[tiab] OR lower extremit*[tiab] OR upper extremit*[tiab] OR lower limb*[tiab] OR upper limb*[tiab] OR ankle*[tiab] OR foot[tiab] OR feet[tiab] OR knee*[tiab] OR hip*[tiab] OR femor*[tiab] OR femur[tiab] OR tibia*[tiab] OR fibula*[tiab] OR calcane*[tiab] OR shoulder*[tiab] OR arm[tiab] OR arms[tiab] OR elbow*[tiab] OR wrist*[tiab] OR hand[tiab] OR hands[tiab] OR leg[tiab] OR legs[tiab]) AND (“Surgical Procedures, Operative”[Mesh] OR “surgery”[Subheading] OR “Orthopedic Procedures”[Mesh] OR invasive procedure*[tiab] OR orthopedic*[tiab] OR orthopaedic*[tiab] OR arthroplast*[tiab] OR knee replac*[tiab] OR surger*[tiab] OR operat*[tiab] OR preoperat*[tiab]) AND (“Pharmacokinetics”[Mesh] OR “pharmacokinetics” [Subheading] OR “Tissue Distribution”[Mesh] OR concentration*[tiab] OR tissue distribution*[tiab] OR tissue locali*[tiab] OR pharmacokinetic*[tiab] OR pharmacokinetic*[tiab] OR absorption*[tiab] OR kinetic*[tiab] OR drug body relation*[tiab])

or foot or feet or knee* or hip* or femor* or femur or tibia* or fibula* or calcane* or shoulder* or arm or arms or elbow* or wrist* or hand or hands or leg or legs).ti,ab,kw. 2,376,346

3 exp surgery/ or su.fs. or exp orthopedic surgery/ or exp total arthroplasty/ or exp knee replacement/ or (invasive procedure* or orthopedic* or orthopaedic* or arthroplast* or knee replac* or surger* or operat* or preoperat*).ti,ab,kw. 5,840,574

4 exp pharmacokinetics/ or pharmacokinetics.fs. or tissue distribution/ or (concentration* or tissue distribution* or tissue locali* or pharmacokinetic* or pharmaco-kinetic* or absorption* or kinetic* or drug body relation*).ti,ab,kw. 3,236,447

5 1 and 2 and 3 and 4 588

Cochrane Library (43 hits):

ID Search

- #1 cephalospor* or kefzol or cefazolin or cephazolin or cefamandole or cefuroxime or duricef or keflex or Cefadroxil or velosef or biocef or panixine or cephalixin or ancef or cephradine or ultracef:ti,ab,kw (Word variations have been searched)
- #2 MeSH descriptor: [Podiatry] explode all trees
- #3 orthopedic* or orthopaedic* or joint* or lower extremit* or upper extremit* or lower limb* or upper limb* or ankle* or foot or feet or knee* or hip* or femor* or femur or tibia* or fibula* or calcane* or shoulder* or arm or arms or elbow* or wrist* or hand or hands or leg or legs:ti,ab,kw (Word variations have been searched)
- #4 #2 or #3
- #5 invasive procedure* or orthopedic* or orthopaedic* or arthroplast* or knee replac* or surger* or operat* or preoperat*:ti,ab,kw (Word variations have been searched)
- #6 concentration* or tissue distribution* or tissue locali* or pharmacokinetic* or pharmaco-kinetic* or absorption* or kinetic* or drug body relation*:ti,ab,kw (Word variations have been searched)
- #7 #1 and #4 and #5 and #6

Embase (Ovid)

#	Searches	Results
1	exp cephalosporin derivative/ or (cephalospor* or kefzol or cefazolin or cephazolin or cefamandole or cefuroxime or duricef or keflex or Cefadroxil or velosef or biocef or panixine or cephalixin or ancef or cephradine or ultracef).ti,ab,kw.	207,766
2	exp lower limb/ or exp upper limb/ or podiatry/ or exp ankle fracture/ or exp “bones of the leg and foot”/ or exp “bones of the arm and hand”/ or exp joint/ or (orthopedic* or orthopaedic* or joint* or lower extremit* or upper extremit* or lower limb* or upper limb* or ankle*	

Table 3. Soft tissue target site cefazolin concentrations

Site	Author (year)	n/dose	Time of sample min (SD)	Concentration µg/g (SD)
Hip capsule	Parsons et al. (1978)	6/4 g	64 (26)	35 (24)
Knee	Cunha et al. (1984)	13/1 g	ND	8 mg/L
	Friedman et al. (1990) ^a	24/1 g	10	75%
			30	57%
			60	54%
	Young et al. (2013)	11/1 g	26 (23)	11 (2.4)
Shoulder	Miller et al. (2004)	7/1 g	40	11

^a See Table 3. ND = not data

Figure 2. Risk of bias analysis, according to Newcastle–Ottawa Scale (NOS) (Wells et al 2013).
 +: low risk of bias/good quality,
 -: high risk of bias/poor quality,
 ?: unknown risk of bias/unclear or not applicable (e.g., comparability of cohorts in studies where only one group received intravenously administered cefazolin).
 A green “+” matches with a star on the NOS.

	Representative cohort	Selection comparative cohort	Ascertainment of exposure	Outcome not present at start	Comparability of cohorts	Comparability of cohorts 2	Assessment of outcome	Duration follow-up	Adequacy follow-up
Angthong (2015)	+	+	+	+	+	+	+	+	+
Bryan (1988)	+	+	+	+	+	+	+	+	+
Cunha (1977/1984)	+	?	?	+	?	+	+	?	?
Deacon (1996)	+	?	?	+	?	+	+	+	?
Friedman (1990)	+	+	?	+	+	+	+	+	?
Miller (2004)	+	?	?	+	?	+	+	+	?
Parsons (1978)	+	?	?	+	?	+	+	+	?
Polk (1983)	+	?	?	+	?	+	+	+	+
Sharareh (2016)	+	+	?	+	?	+	+	+	?
Sorensen (1978)	+	?	?	+	?	+	+	+	?
Williams (1983)	+	+	+	+	+	+	+	+	?
Yamada (2011)	+	+	?	+	+	+	+	+	+
Young (2012)	+	?	?	+	?	+	+	+	?

Table 4. Antibiotic concentrations organized by location of target site

Author (year)	Site	n/dose	Time of sample min (SD)	Concentration µg/g (SD)
Angthong et al. (2015)	Hip	14/1 g	52 (7)	22 (10)
	Hip	7/2 g	63 (23)	40 (16)
Bryan et al. (1988)	Hip	31/1 g	118 (49)	1.6 (1.4)
Cunha et al. (1977)	Hip	ND/1 g	40	30
Parsons et al. (1978)	Hip ^b	6/4 g	61 (31)	10 (2.9)
	Hip ^c	12/4 g	64 (26)	14 (2.3)
	Hip ^d	3/4 g	37 (28)	15 (3.3)
	Hip ^e	14/4 g	74 (30)	88 (23)
Polk et al. (1983)	Hip	9/ ^f	53 (20)	7.7 (4.8)
Sharareh et al. (2016)	Hip	11/1&2 g	ND	12 (6.7)
Sorensen et al. (1978)	Hip	1/1 g	45	12
Williams et al. (1983)	Hip	9/1 g	ND	6.9 (1.3)
		4/2 g	ND	18
Yamada et al. (2011)	Hip	16/2 g	64 (33)	32 (15)
Bryan et al. (1988)	Knee	11/1 g	107 (39)	0.64 (0.57)
Cunha et al. (1984)	Knee	13/1 g	30	11
Friedman et al. (1990) ^a	Knee	24/1 g	10	20%
			30	40%
			60	39%
Sharareh et al. (2016)	Knee	20/1&2 g	ND	6.0 (3.6)
Williams et al. (1983)	Knee	8/1 g	ND	4.7 (2.4)
		2/2 g	ND	7.8
Yamada et al. (2011)	Knee	27/2 g	63 (19)	16 (10)
Young et al. (2013)	Knee	11/1 g	34 (20)	11 (2.5)
Deacon et al. (1996)	Foot	25/1 g	70	2.4
Miller et al. (2004)	Shoulder	7/1 g	40	36

^a Multiple samples, results are in percentage of patients achieving a concentration > 4 µg/g (MIC).

^b acetabulum, ^c proximal femur, ^d cortical shaft, ^e hip ground up

^f 10 mg/kg

ND = not data

Table 5. Antibiotic bone concentrations organized by dose

Dose	Author (year)	Site	n	Time of sample min (SD)	Concentration µg/g (SD)
Cefazolin 1 g					
	Angthong et al. (2015)	Hip	14	52 (7)	22 (10)
	Bryan et al. (1988)	Hip	31	118 (49)	1.6 (1.4)
		Knee	11	107 (39)	0.64 (0.57)
	Cunha et al. (1977)	Hip	ND	40	30
	Cunha et al. (1984)	Knee	13	30	11
	Deacon et al. (1996)	Foot	25	70	2.4
	Friedman et al. (1990) ^a	Knee	24	10	20%
				30	40%
				60	39%
	Miller et al. (2004)	Shoulder	7	40	36
	Sharareh et al. (2016)	H&K	4	ND	5.0 (3.1)
	Sorensen et al. (1978)	Hip	1	45	12
	Williams et al. (1983)	H&K	17	69	5.9
	Young et al. (2013)	Knee	11	34 (20)	11 (2.5)
Cefazolin 2 g					
	Angthong et al. (2015)	Hip	7	63 (23)	40 (16)
	Sharareh et al. (2016)	H&K	27	ND	8.3 (5.6)
	Williams et al. (1983)	H&K	6	51	15
	Yamada et al. (2011)	H&K	42	63 (25)	22 (15)
Other dose					
	Polk et al. (1983) ^f	Hip	9	53 (20)	7.7 (4.8)
	Parsons et al. (1978) ^g	Hip ^b	6	61 (31)	10 (2.9)
		Hip ^c	12	64 (26)	14 (2.3)
		Hip ^d	3	37 (28)	15 (3.3)
		Hip ^e	14	74 (30)	88 (23)

^a See Table 3

^b acetabulum, ^c proximal femur, ^d cortical shaft, ^e hip ground up

^f 10 mg/kg, ^g Cefazolin 4 g

H&K = Hip and knee

ND = not data

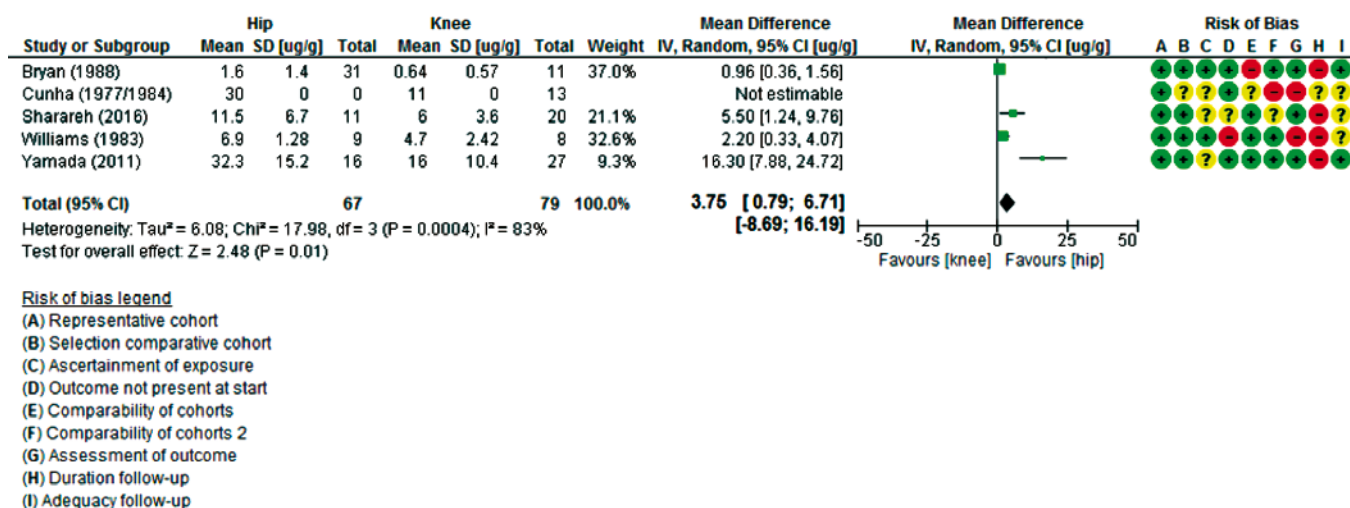


Figure 5. Pooled results: mean target site concentrations compared by location of measurement.

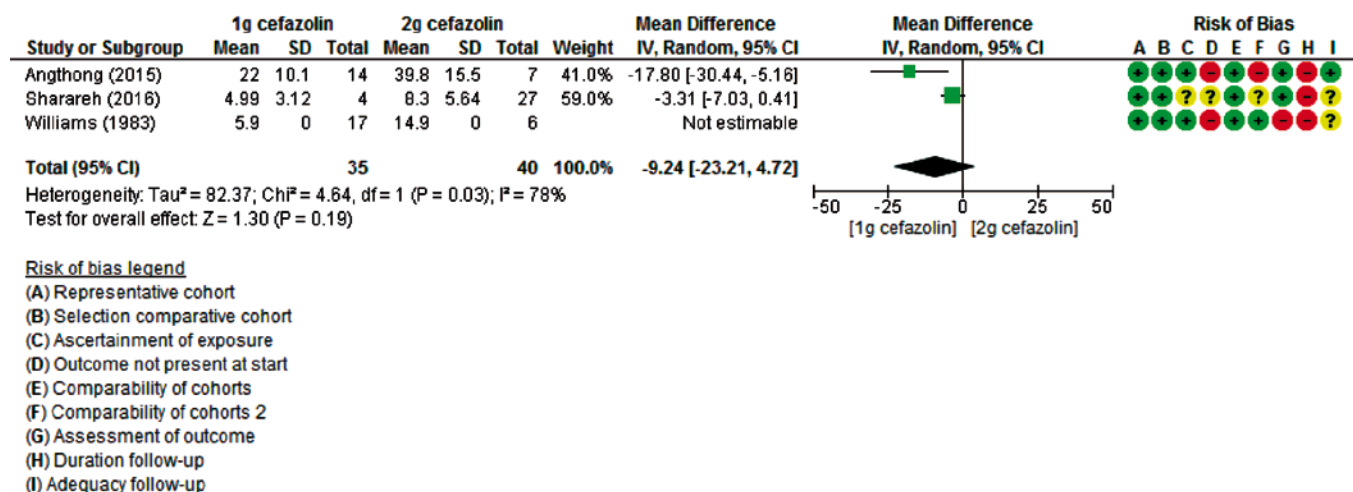


Figure 6. Pooled results: mean target site bone concentrations compared by dose. Due to the small number of studies for this outcome, no predictive interval was computed

Adjusted rating sheet Newcastle–Ottawa quality assessment scale for cohort studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

A star on the NOS is counted as a point and depicted as a green “+” in Figure 2. A red “–” stands for a high risk of bias (no “*” on the rating sheet) and an orange “?” is either something that is not described, or not applicable.

Selection

(1) Representativeness of the exposed cohort

- (a) truly representative of the average patient undergoing orthopaedic surgery of the limb in the community *
- (b) somewhat representative of the average patient undergoing orthopaedic surgery of the limb in the community *
- (c) selected group of users eg nurses, volunteers
- (d) no description of the derivation of the cohort

(2) Selection of the non-exposed cohort or comparative group

- (a) drawn from the same community as the exposed cohort *
- (b) drawn from a different source
- (c) no description of the derivation of the non-exposed cohort

(3) Ascertainment of exposure

- (a) secure record (e.g., surgical records) *
- (b) structured interview *
- (c) written self-report
- (d) no description

(4) Demonstration that outcome of interest was not present at start of study

- (a) yes * (exclusion of patients receiving antibiotics before measurement at baseline)
- (b) no

Comparability

(1) Comparability of cohorts on the basis of the design or analysis

- (a) study controls for baseline characteristics (age, weight) *
- (b) study controls for analysis (comparable measurements, eg time point) *

Outcome

(1) Assessment of outcome (blinding/quality of analysis)

- (a) independent blind assessment + HPLC *
- (b) record linkage/unblinded HPLC *
- (c) self-report/other analysis method (e.g., agar disk diffusion method)
- (d) no description

(2) Was follow-up long enough for outcomes to occur?

- (a) yes (measurements throughout full duration of the surgery) *
- (b) no

(3) Adequacy of follow up of cohorts

- (a) complete follow-up—all subjects accounted for *
- (b) subjects lost to follow-up unlikely to introduce bias—small number lost (< 10 % follow-up, or description provided of those lost) *
- (c) lost to follow-up (rate > 10% and no description of those lost)
- (d) no statement