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Appendix

TABLE E-1 Search Terms

Category	Search Terms*
Disease	(Chronic) osteomyelitis, osteitis, bone infection
Antibiotics	Gentamicin, vancomycin, anti-infective agent, (local) antibiotics
Properties	Drug delivery systems, collagen, Sulmycin-implant, collagen fleece, collagen sponge, antibiotic loaded sponge, antibiotic loaded fleece, Sulmycin
Brands	Garacoll, Garacol, Garamycin, Sulmycin, Duracoll, Cronocol, Gentacoll, Septocoll

*This table lists all important search terms. These search terms were applied in different ways depending on which database was being searched. In the MEDLINE (PubMed) search, they were used as MeSH (Medical Subject Heading) terms or as general search terms. In Embase (OVID), some of these terms were used as explored subject headings (exp) or as general terms. In the Cochrane library, only general search terms ([chronic] osteomyelitis, collagen, and collagen fleece) were used to identify Cochrane reviews in this particular research area.

Search Strategy, MEDLINE (PubMed)

1. Osteomyelitis [MeSH]
2. Osteitis [MeSH]
3. Bone infection [MeSH]
4. Osteomyelitis
5. Osteitis
6. Bone infection
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
8. Drug delivery systems [MeSH]
9. Collagen [MeSH]
10. Collagen sponge
11. Collagen fleece
12. Antibiotic loaded sponge
13. Antibiotic loaded fleece
14. Sulmycin-implant [Supplementary Concept]
15. Sulmycin
16. 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
17. Vancomycin [MeSH]
18. Gentamicins [MeSH]
19. Anti-infective agents [MeSH]
20. Vancomycin
21. Gentamicin
22. Antibiotics
23. 17 OR 18 OR 19 OR 20 OR 21 OR 22
24. 7 AND 16 AND 23

Search Strategy, Embase (OVID)

1. Garacol.mp.
2. Garacoll.mp.
3. Sulmycin.mp.
4. Garamycin.mp.
5. Duracoll.mp.
6. Cronocol.mp.
7. Gentacoll.mp.

8. Septocoll.mp.
9. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
10. exp collagen/
11. collagen.mp.
12. collagen fleece.mp.
13. exp collagen sponge/
14. collagen sponge.mp.
15. local antibiotics.mp.
16. 10 OR 11 OR 12 OR 13 OR 14 OR 15
17. exp osteomyelitis/
18. exp chronic osteomyelitis/
19. exp bone infection/
20. osteomyelitis.mp.
21. chronic osteomyelitis.mp.
22. bone infection.mp.
23. 17 OR 18 OR 19 OR 20 OR 21 OR 22
24. 9 OR 16
25. 23 AND 24

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TABLE E-2 General Criteria for Assessing Risk of Bias in a Study

Domain	Support for Judgment
Definition and generation of study groups	Inclusion and exclusion criteria. Definition of study group(s). Baseline characteristics of study groups mentioned. Analysis between baseline characteristics of treatment and control group, method of diagnosis
Intervention (and control treatment)	Well-defined treatment (and control) protocols. Important differences between groups in case these can influence outcomes. Other types of exposures/additional treatments
Allocation of treatment	Randomization. Other methods of allocation. Possible risks for selection bias
Confounding	Any confounding factors in the intervention. Possibility of confounding factors before treatment. Method of diagnosis of patients. Classification of severity of osteomyelitis/infection
Blinding	Enrollment of patients. Single or double blinding. Blinding for outcome analysis
Assessment of outcome measurement	Outcome definitions. Used outcome measures. Compliance with outcome measures. Subjective outcome measures
Follow-up	Follow-up period. Withdrawals or loss to follow-up. Explanation for loss of patients. Intention-to-treat (ITT) or per-protocol (PP) analysis
Outcome reporting	Completeness of outcome reporting. Missing data. Discussion of outcomes. Reporting and explanation of failure of treatment. Complications and adverse events
Protocol compliance	Changes in protocol. Other types of treatment/interventions before analysis. Other types of treatment/interventions after analysis
Other sources of bias	Statistical analysis performed. P values given (if statistical analysis performed). Study design-related factors of bias. Contamination of treatments

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TABLE E-3 Assessment of Risks of Bias in Each Individual Study

Ascherl et al. 1990[24]: [Local Treatment of Infection with Collagen Gentamicin]		
Domain	Support for Judgment	Review Authors' Judgment
Definition and generation of study groups	Unclear inclusion and exclusion criteria. Patients with chronic osteomyelitis and periprosthetic joint infections (PJIs) mixed. Only 27 chronic osteomyelitis patients. No baseline characteristics. No methods of diagnosis described	−
Intervention (and control treatment)	Intervention clearly described. No control group. Used materials clearly described	±
Allocation of treatment	No randomization. No other allocation described	−
Confounding	No description of interventions before treatment. No classification of patients' osteomyelitis severity. No clear method of diagnosis described. No confounding co-interventions described	−
Blinding	No treatment blinding. No outcome assessor blinding described	−
Assessment of outcome measurement	Good outcome measurement. Unclear and incomplete outcome description. Well-described secondary outcome measurements (pharmacokinetics and toxicity)	±
Follow-up	4 years' follow-up; loss to follow-up, 13 patients, not explained	±
Outcome reporting	Missing data or poor description of outcomes. No complications or side-effects mentioned	−
Protocol compliance	No clear mention of compliance with protocol or whether intention-to-treat or per-protocol analysis was used. Poor intervention protocol, which is susceptible to bias	−
Other sources of bias	No statistical analysis. Multiple publications on same study group without clear explanation about differences	±

Buehler et al. 2002[25]: Controlled, Single-Blind, International, Multicentre Study on the Efficacy and Tolerability of Gentamicin-Collagen-Fleece Septocoll® in Subjects with Autologous Cancellous Bone Grafts Following Chronic Osteomyelitis and/or Infected Non-Union		
Domain	Support for Judgment	Review Authors' Judgment
Definition and generation of study groups	No clear inclusion and exclusion criteria. No description of diagnosis, 123 patients having chronic osteomyelitis were included from 23 medical centers. Baseline characteristics clearly mentioned in an additional table	±
Intervention (and control treatment)	Clear intervention and control protocols. Comparable control groups. No risks of important treatment differences between groups. Description of intervention lacks the number of collagen fleeces (sponges)	±
Allocation of treatment	Patients were randomly assigned to 1 of the 2 treatment groups (n = 62 in Septocoll group, n = 61 in control group)	+
Confounding	The authors mention that the demographic characteristics and location of osteomyelitis were comparable in both groups. In addition, the groups did not show significant differences regarding history, physical constitution, underlying diseases, and severity of osteomyelitis. Furthermore, administration of antibiotics during operation was not permitted	+
Blinding	This RCT is single-blinded (only the participant was blinded; personnel and outcome assessors were not blinded)	+
Assessment of outcome measurement	Good outcome definition, good and clear outcome measures. No subjective outcome measures	+
Follow-up	Follow-up period was only 6 weeks. 93 of 123 patients finished the study according to the protocol so 30 patients were lost to follow-up, for reasons not mentioned	−
Outcome reporting	Complete outcome reporting. Infection rates were calculated according to both intention-to-treat and per-protocol analyses with regard to the loss-to-follow-up	+

Protocol compliance	Protocols were precisely written and checked by several ethical and clinical practice committees before these were sent to the 23 different medical centers. Study protocol was, in our opinion, maintained as strictly as possible in the analyzed patients; since the number of analyzed patients (123) was already low compared with the sample size of 188 patients, 30 of the 123 patients were included in the analysis but classified as having had treatment that was "not according to protocol" (with the remaining 93 patients finishing the study exactly according to protocol)	+
Other sources of bias	Only chi-square test is mentioned. Further statistical analysis is not described. Study was terminated prematurely because of inability to reach number of patients needed	±

von Hasselbach 1989[26]: [Clinical Aspects and Pharmacokinetics of Collagen-Gentamicin as Adjuvant Local Therapy of Osseous Infections]		
Domain	Support for Judgment	Review Authors' Judgment
Definition and generation of study groups	Population with chronic osteomyelitis and PJIs. Unclear inclusion and exclusion criteria. Large study population of 58 chronic osteomyelitis patients in a single cohort. Moderately well described baseline characteristics	±
Intervention (and control treatment)	The intervention could have been described in more detail. No control group. Used implants are well described. Number of implanted sponges not mentioned	±
Allocation of treatment	No randomization. No allocation described	−
Confounding	Unclear description of possible interventions before treatment. No disease classification of patients. No description of confounding factors involving intervention	±
Blinding	No treatment blinding. No outcome assessor blinding described	−
Assessment of outcome measurement	Outcomes unclearly defined. Primary outcome measures unclear. Clear secondary outcome measures	−
Follow-up	Good mean follow-up of 13.7 months. Loss to follow-up of 25 patients after 1 year, unexplained	±
Outcome reporting	Extensive reporting of pharmacokinetics. Fair reporting of primary outcome. Missing data. Good reporting of adverse events/complications	±
Protocol compliance	Unclear protocol compliance. No additional treatments of patients in analysis	±
Other sources of bias	No statistical analysis. Many different locations, which might yield a lot of variation in treatment algorithms, which is not mentioned	−

Dieckmann et al. 2008[27]: [Treatment of Acute and Chronic Osteomyelitis in Children]		
Domain	Support for Judgment	Review Authors' Judgment
Definition and generation of study groups	Clear definition of populations. Good description of diagnostic methods. No clear inclusion or exclusion criteria. Good population of 53 patients with chronic osteomyelitis. Description of baseline characteristics	±
Intervention (and control treatment)	2 different groups. Treatment group received sponges, control group received gentamicin-loaded PMMA beads. Clear description of treatment group protocol. Unclear exactly what treatment of control group consisted of	±
Allocation of treatment	No randomization. Allocation of patients to treatment groups unclear; authors only mentioned that patients with greater disease severity were allocated to not receive sponges	−
Confounding	More severe patients received other treatment. Well-described differences between acute and chronic osteomyelitis patients. No additional treatment mentioned	±
Blinding	No treatment blinding. No outcome assessor blinding described	−

Assessment of outcome measurement	Good and sufficient outcome measures for primary outcome. Outcomes well defined	+
Follow-up	Good mean follow-up of 85.2 months. No loss to follow-up in this retrospective study design	+
Outcome reporting	Outcomes described well, but could be described more extensively. Extensive reporting of complications/failures	±
Protocol compliance	Unclear protocol compliance, no additional treatments described for primary analysis	±
Other sources of bias	No statistical analysis. Retrospective design. No contamination of treatment	±

Feil et al. 1990[28]: [Bioresorbable Collagen-Gentamicin Compound as Local Antibiotic Therapy]		
Domain	Support for Judgment	Review Authors' Judgment
Definition and generation of study groups	Unclear definition of study group. Unclear inclusion and exclusion criteria. A total of 64 patients with osteomyelitis, or PJIs (5). Well-described baseline characteristics. Unclear diagnostic methods	±
Intervention (and control treatment)	Clear and complete description of intervention. No control group. Good description of therapy used in addition to sponges	+
Allocation of treatment	No randomization, Allocation not described. No allocation differences between different pathologies	−
Confounding	Unclear which interventions took place before study treatment. No other confounding factors described	±
Blinding	No treatment blinding. No outcome assessor blinding described	−
Assessment of outcome measurement	Unclear definition of eradication of infection and which methods were used. Good measurement protocols for pharmacokinetics	±
Follow-up	Mean follow-up of 1 year. 5 patients lost to follow-up, well described and explained as not related to treatment	±
Outcome reporting	Missing data. Primary outcome unclearly measured. Subgroup analysis in secondary outcome. Complications fairly well described	−
Protocol compliance	No clear protocol compliance. No other treatments described that influence outcomes	±
Other sources of bias	No statistical analysis. No other sources of bias	±

Ipsen et.al 1991[29]: Gentamicin-Collagen Sponge for Local Applications. 10 Cases of Chronic Osteomyelitis Followed for 1 Year		
Domain	Support for Judgment	Review Authors' Judgment
Definition and generation of study groups	Well-described study population. Well-described inclusion and exclusion criteria. Small study population of 10 patients. Good baseline characteristics	+
Intervention (and control treatment)	Clear intervention protocol. Good description of implants used. Good description of treatments used in addition to sponges	+
Allocation of treatment	No randomization. Allocation of treatment not described	−
Confounding	No confounding factors described. No classification of patients mentioned	±
Blinding	No treatment blinding. No outcome assessor blinding described	−
Assessment of outcome measurement	Methods of measurement of gentamicin concentrations are clearly described, including specific manufacturers. In addition, times of sample collection are clearly described. However, clinical symptoms of osteomyelitis are not specifically described	±
Follow-up	Follow-up of 12 months. No loss to follow-up	±
Outcome reporting	The result section is brief and some data were missing for a really small study population	−
Protocol compliance	Protocols are described and outcome measures seem not to deviate from that protocol	+

Other sources of bias	No statistical analysis performed. No other bias was detected	±

Kwasny et.al 1994[30]: The Use of Gentamicin Collagen Floss in the Treatment of Infections in Trauma Surgery		
Domain	Support for Judgment	Review Authors' Judgment
Definition and generation of study groups	49 patients having postoperative or posttraumatic osteitis were included. Neither patients' baseline characteristics nor specific inclusion and exclusion criteria described. No description of diagnostic methods	−
Intervention (and control treatment)	The gentamicin-collagen sponge was used as adjunct therapy. Treatment is not further specified. Neither the brand of the collagen sponge nor the number of flosses used is described. No control group	−
Allocation of treatment	No description of randomization or how the treatment was allocated	−
Confounding	No information about possible confounders, no classification of patients	±
Blinding	No treatment blinding. No outcome assessor blinding described	−
Assessment of outcome measurement	Standard outcome measures. Specific clinical symptoms of infection not described. Pharmacokinetics well described	±
Follow-up	Follow-up is documented and briefly described (20 months average, minimum follow-up = 6 months). No loss to follow-up	+
Outcome reporting	In the context of a case series report, information is not selectively reported	+
Protocol compliance	Compliance with protocol not described. No additional treatment that can influence outcomes mentioned	±
Other sources of bias	No statistical analysis. No other bias detected	±

Letsch et al. 1993[31]: [Local Antibiotic Administration in Osteomyelitis Treatment–A Comparative Study with Two Different Carrier Substances]		
Domain	Support for Judgment	Review Authors' Judgment
Definition and generation of study groups	Clear population definition. Clear inclusion and exclusion criteria. 2 relatively small groups of 10 versus 10 patients. Good description of baseline characteristics	+
Intervention (and control treatment)	Intervention and controls well described. Clear protocols. 2 groups: gentamicin sponges and gentamicin-loaded PMMA beads. Clearly description of which materials were used. No description of number of sponges or beads per patient	+
Allocation of treatment	1:1 randomization. No stratification applied	+
Confounding	Patients received some treatments just before their interventions, but not clearly explained. No other confounding factors	±
Blinding	No treatment blinding. No outcome assessor blinding described	−
Assessment of outcome measurement	Clear outcome definitions. Clear primary and secondary outcome measures. No subjective outcomes	+
Follow-up	Mean follow-up of 16.2 months. No loss to follow-up described	+
Outcome reporting	Despite good measures, poorly described outcomes in a brief result section. Selective reporting of pharmacokinetic outcomes	±
Protocol compliance	Compliance with protocol, but some additional treatments within the interventions	±
Other sources of bias	Statistical analysis performed, but test not mentioned and no p values mentioned	−

Leung et al. 2015[32]: The Effectiveness of Local Antibiotics in Treating Chronic Osteomyelitis in a Cohort of 50 Patients with an Average of 4 Years Follow-up

Domain	Support for Judgment	Review Authors' Judgment
Definition and generation of study groups	Clearly defined patient population. No clear inclusion and exclusion criteria. 50 patients in 1 single cohort with chronic osteomyelitis. Good baseline description. Unclear diagnostic measures	±
Intervention (and control treatment)	Intervention poorly described. Historical control group used for comparison, but no data for this group described. Investigational product clearly described	±
Allocation of treatment	No randomization. Allocation not mentioned	−
Confounding	Unclear previous interventions before treatment. No other sources of confounding	±
Blinding	No treatment blinding. No outcome assessor blinding described	−
Assessment of outcome measurement	Good outcome definitions. Good outcome measures. No subjective measures	+
Follow-up	Mean follow-up 38.4 months. No loss to follow-up	+
Outcome reporting	Some missing data about intervention. Well-described outcome. Failures and complications well described	±
Protocol compliance	Some deviations from protocol, but unclear why. In general, good compliance	±
Other sources of bias	No statistical analysis. Probable bias introduced by historical control group	±

Wernet et al. 1992[18]: [Antibiotic-Containing Collagen Sponge in Therapy of Osteitis]		
Domain	Support for Judgment	Review Authors' Judgment
Definition and generation of study groups	Good definition of study population. No clear inclusion or exclusion criteria. Good group size with 47 chronic osteomyelitis patients. No baseline characteristics described. No diagnostic methods described	±
Intervention (and control treatment)	Clear intervention protocol. Good description of materials. No control group, but subgroups for pharmacokinetics	±
Allocation of treatment	No randomization, no other allocation described	−
Confounding	Additional treatment for wound exudation. No previous interventions before study treatment described	±
Blinding	No treatment blinding. No outcome assessor blinding described	−
Assessment of outcome measurement	Good description of primary outcome and secondary outcomes. No outcome measures described	±
Follow-up	Neither follow-up period nor loss to follow-up is described	−
Outcome reporting	Clear outcome reporting on both outcomes	+
Protocol compliance	No compliance described, but no treatment that affects primary or secondary outcomes or introduces bias	±
Other sources of bias	No statistical analysis, no other sources of bias	±