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A Scoping Review on the Use of Antibiotic-Impregnated Beads and Applications to Vascular Surgery

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Abstract

Introduction: Surgical site infection (SSI) presents a ubiquitous concern to surgical specialties, especially in the presence of prosthetic material. Antibiotic-impregnated beads present a novel and evolving means to combat this condition. This review aims to analyze the quality of evidence and methods of antibiotic bead use, particularly for application within vascular surgery. **Methods:** A systematic scoping review was conducted within Embase, MEDLINE, and the Cochrane Registry of Randomized Controlled Trials. Articles were evaluated by 2 independent reviewers. Level of evidence was evaluated using the Oxford Center for Evidence-Based Medicine Criteria and the Cochrane Risk of Bias Tool for Randomized Controlled Trials. **Results:** The search yielded 6951 papers, with 275 included for final analysis. Publications increased in frequency from 1978 to the present. The most common formulation was polymethyl methacrylate; however publications on biodegradable formulations, including calcium sulfate beads, have been published with increasing frequency. Most publications had positive conclusions (94.2%); however, the data was mainly subjective and may be prone to publication bias. Only 11 randomized controlled trials were identified and all but one was evaluated to be at a high risk of bias. The most common indication was for osteomyelitis (52%), orthopedic prosthetic infections (20%), and trauma (9%). Within vascular surgery, beads have been used primarily for the treatment of graft infection, with freedom from recurrence rates being reported from 41% to 87.5%. **Conclusions:** Antibiotic-impregnated beads provide a means to deliver high doses of antibiotic directly to a surgical site, without the risks of parenteral therapy. There has yet to be significant high-level quality data published on their use. There is a large body of evidence that suggests antibiotic beads may be used in SSIs in high-risk patients, prosthetic infections, and other complex surgical infections. Important potential areas of application in vascular surgery include graft infection, prevention of wound infection in high-risk patients, and diabetic foot infection.

Keywords

vascular surgery, antibiotic beads, graft infection, surgical site infection, polymethyl methacrylate, prosthesis-related infections, diabetic foot infection

Introduction

Surgical site infections (SSIs) are a ubiquitous concern to all surgical specialties. The Center for Disease Control (CDC) quotes a 2% to 5% risk for clean procedures.[1] Higher rates are reported in traumatic injuries (20%-50%) or in some elective populations, including high-risk vascular surgery patients (15% or greater).[2-6] Surgical site infection can significantly increase cost and morbidity.[1] Morbidity, however, can be magnitudes higher when it involves prosthetic material. The increasing use of prosthetic devices across surgical specialties moves prevention and treatment of surgical infections to the forefront of clinical significance.

Current CDC guidelines for clean procedures recommend no more than 24 hours of intravenous (IV) antibiotics post-operatively, as there has been no proven benefit past this time interval.[7] When it comes to established infection either requiring surgical intervention or involving a surgical prosthesis, there is less established literature to draw from. While exact indications are yet to be fully defined, there continues to be active interest in novel methods of antibiotic delivery, such as pastes, powders, beads, and sponges.[3,8]

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Antibiotic beads were first described in Europe in the 1970s.[9] They originated within orthopedics as a means to provide a depot source of antibiotic into an infected surgical field.[9] They subsequently were described in osteomyelitis (OM) management; in prosthetic infections in vascular, cardiac, and orthopedic surgery; and in traumas and contaminated fields.[8,10,11] Unlike powders, pastes, and sponges, antibiotic beads are retained for a longer period of time and therefore allow for an extended period of antibiotic release.[12-14]

The initial formulation consisted of polymethyl methacrylate (PMMA), a bone cement, which was mixed with antibiotic powder and formed into a chain of beads. These beads either had to be left indefinitely or removed at a subsequent surgical procedure. This has driven the development of biodegradable formulations of antibiotic-impregnated beads, with $CaSO_4$ being the best described. These beads achieve the same result of delivering high antibiotic concentrations to a local surgical site, however will dissolve over a period of months.[13,15]

Scoping reviews act as a means to explore and synthesize a diverse body of research with a significant amount of heterogeneity.[16] While performed in a systematic fashion, it is not limited in terms of its breadth as is seen with meta-analysis.[16] This was therefore the ideal format for our review which explores evidence across many fields and indications. This article aims to identify and map the existing literature regarding antibiotic-impregnated beads and identify gaps in the literature. By exploring and defining the current applications of antibiotic-impregnated beads, we then explore how this can be translated into practice within vascular surgery.

Methods

We conducted a scoping review, in systematic fashion, targeting all published literature regarding antibiotic-impregnated beads in surgery. A broad search of the literature was constructed and tested against known papers of interest to ensure an adequate scope (Appendix A, Appendix B). The final search was executed on May 7, 2017, including Embase 1974 to May 5, 2017, and OVID MEDLINE Epub Ahead of Print, In-process, and other nonindexed citations, Ovid MEDLINE. The Cochrane Central Register of Controlled Trials was searched separately using a similar search strategy. Duplicates were removed from within each database search using OVID. Results from Medline and Embase were exported to RefWorks to remove duplicates between the 2 databases. All results from the Cochrane Registry were reviewed and duplicates hand removed by the authors.

The initial 300 articles were used as a pilot to train reviewers. The remaining articles were reviewed by 2 independent reviewers (B.M. and K.P.A.) using the predefined inclusion and exclusion criteria below.

Inclusion criteria

1. Articles included antibiotic-impregnated beads, pellets, tablets, or other synonyms.
2. New description of use in a clinical setting with direct application to tissues.

Exclusion criteria

1. Animal studies or in vitro studies.
2. Any language other than English.
3. Full text unavailable for access using the McMaster University library system.
4. Other delivery systems such as sponges, fleeces, powders, liquids.
5. Any study involving only ingestion of the antibiotic-impregnated carrier.
6. Any article not reporting new clinical outcomes; reviews in which authors do not present any new cases.

Papers were initially screened by title and abstract. Articles where it was ambiguous whether they met inclusion from title and abstract alone were reviewed in full. Disagreements were discussed among the reviewers. A decision was made between the 2 screening authors in all cases.

Articles were then reviewed in full for data abstraction using a standardized data collection form. The Oxford Centre for Evidence-Based Medicine criteria were used to define the level of evidence.[17] The Cochrane Risk of Bias Tool for Randomized Controlled Trials was used to analyze risk of bias in randomized controlled trials (RCTs).[18]

Outcomes of interest included general characteristics (year, country and field of publication, conflict of interest, target disease process), study methodology (type of study, level of evidence), and study details (number of participants, outcomes of interest, systemic antibiotic use, antibiotic carrier used, antibiotic choice, length of follow-up, general conclusions). Data analysis was conducted using Microsoft Excel 2017 (version 16.9) and using SAS software, version 9.4. Descriptive statistics were used in order to examine all outcomes of interest. Distribution of the data was first analyzed and data following a normal distribution were presented as mean with standard deviation. Non-normal data were presented as median with interquartile range.

Results

Search

The search yielded 4033 results in MEDLINE, with 52 duplicates being removed (Figure 1). Embase yielded 5148 results, with 44 duplicates being removed. There were 2136 duplicates between the 2 databases. This left 6951 results for title and abstract review. Search of the Cochrane Registry yielded 136 articles, of which all titles and abstracts were reviewed. Of these articles, 14 met the inclusion criteria, however, all had previously been identified in the search of Embase and MEDLINE.

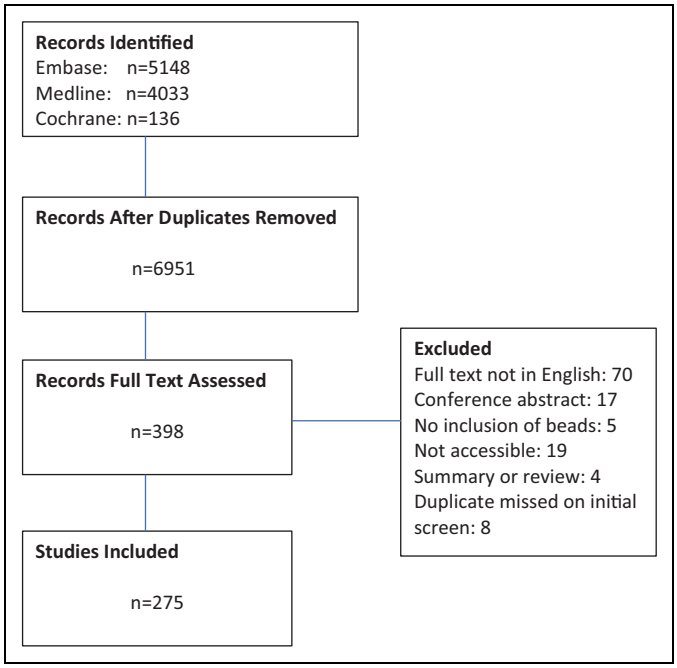

Figure 1. Search strategy. Number of articles identified in Embase, Medline, and the Cochrane registry of randomized controlled trials. Number of articles assessed in full, following abstract screening, for data extraction is given. Reasons for exclusion of articles initially believed to meet criteria from the abstract alone are provided.

There were 115 disagreements between screening authors. Of these, 36 did not have an available full text in English and therefore were excluded. Cohen κ coefficient between the authors was 0.868. Following reconciliation of disagreements between the authors, a total of 398 articles were reviewed in full text for data abstraction. Of these, 123 had met the inclusion criteria based on the abstract, however, were excluded at full text review for the following reasons: no English full text (70), conference abstract only (17), no use of antibiotic beads (5), not accessible (19), no new evidence presented (4), and duplicates missed on initial screening (8). The final number of articles included for data analysis was 275.

Publication Data

The first publication identified in our search was published in 1978, describing the elution of gentamicin from PMMA beads.[9] Sources exist as early as 1970; however, as these are in German, they were excluded from our review. Publications have been increasing since the 1990s (Figure 2), with a mean of 5 (Q1:3, Q3:7) publications per year and a total of 208 articles published on PMMA beads. There has been a total of 35 publications on $CaSO_4$ beads with the first appearing in 2001. There has been at least one publication per year since 2009 with a median of 2.5 (Q1:1, Q3:4) per year. These 2 compositions of antibiotic-impregnated beads made up 81% of articles. Other formulations included $CaCO_3$ (1), $CaPO_4$ (1), hydroxyapatite (4), and composition was not defined in 23 (8%).

As can be seen in Table 1, the most common source of publications was from the United States (34.9%). There is however a substantial amount of literature originating from around the world, with many European and Asian countries contributing large numbers of studies.

Of included articles, the primary focus of the article was antibiotic-impregnated beads in 186 (68%). In the remaining 32% of articles, antibiotic beads were included in the treatment protocol; however, the variable of interest was a different aspect of care.

Level of Evidence

Of studies with beads as their primary focus, 91% were level 4 evidence (Table 2). There was 1 level 3 study published, 21 level 2 studies, and one level 1 study published. Of studies with a level of evidence greater than 4, 91% came from the orthopedics literature. The median number of patients treated was 9 (Q1:1, Q3:25), with 14 studies including greater than 100 patients. Of these, 14 studies (86%) were from the orthopedic literature.

In studies with a focus on antibiotic beads, the majority (74%) of authors made a subjective conclusion that the beads offered some form of benefit (Table 2). Conclusions were based on statistical analysis in 10% of studies. Of these, half (5%) concluded there was a statistically significant benefit and 5% failed to reach statistical significance.

Randomized Controlled Trials

There were 11 randomized controlled studies identified. One of these focused on antibiotic-impregnated bone grafting, with all patients receiving antibiotic beads as an adjunct.[19] Of the remaining 10 studies, there was a significant risk of bias in 9, as shown in Figure 3. There was a multicenter RCT conducted from 1985 to 1990, with the purpose of providing evidence for Food and Drug Administration approval of Septopal (Medtronic Europe, Berlin, Germany).[20] Septopal is a commercially produced gentamicin PMMA bead.[20] The study compared gentamicin PMMA beads to standard IV antibiotic therapy for OM. This however had significant risk of bias and the authors noted that randomization protocol was not adhered to at some sites. Three of the other RCTs identified appear to be published reports of groups within this larger RCT.[21-23]

The remaining 6 RCTs included 3 studies with a comparison of PMMA beads to standard antibiotic therapy in different clinical scenarios: open fractures, infected arthroplasty, and subclinical OM.[24-26] None of these studies demonstrated statistically significant improvement; however, all were likely underpowered and had a significant risk of bias. One study randomized patients to PMMA beads and standard antibiotic therapy post abdominal peroneal resection (APR); however, this too demonstrated a significant risk of bias.[27]

Only one study was considered to have a low risk of bias and was considered level 1 evidence.[15] It was a small study comparing PMMA to $CaSO_4$ beads for the treatment of chronic

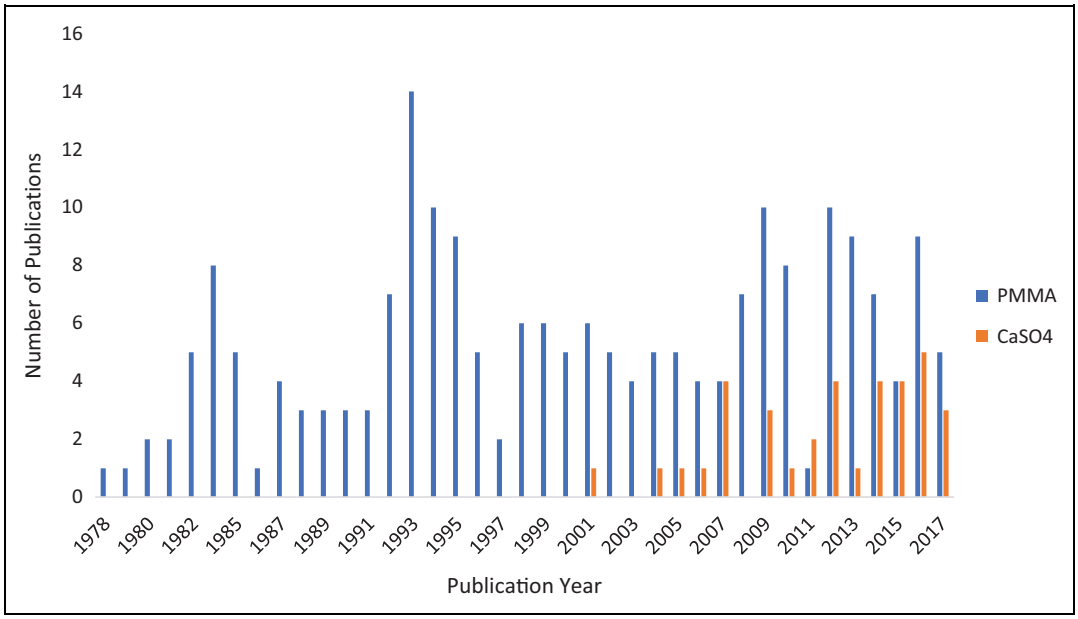

Figure 2. Number of publications over time. The number of publications for both PMMA (blue) and $CaSO_4$ (orange) beads are given for each year. PMMA indicates polymethylmethacrylate.

Table 1. Country of Publication.[a]

Country of Publication	Percent (%)
United States	34.9
United Kingdom	10.8
Germany	9.4
Netherlands	6.1
China	5.8
Japan	4.3
Taiwan	4.3
Sweden	2.1
Korea	1.8
Canada	1.4
Other Europe	10.1
Other Asia	7.6
Other Africa	0.7
Not determined	0.7

[a]Percentage of total published articles originating from a given country. Countries not given by name were grouped into categories by continent.

OM.[15] While there was no statistically significant difference between the groups in terms of recurrence, patients treated with $CaSO_4$ required less frequent reoperation. This study was small, however, and likely underpowered.

Clinical Factors

In 76% of studies, IV antibiotics were used routinely. In only 3% of studies, beads were used with no systemic antibiotics, and in another 3%, only routine perioperative antibiotics were administered. In 11%, patients received additional antibiotic material, such as antibiotic spacers, gentamicin fleece, or antibiotic cement for arthroplasty fixation.

As seen in Figure 4, gentamicin was the only antibiotic used until 1984. There was then a gradual increase in diversity of antibiotic choice. Many sources included preparations with more than one antibiotic. Gentamicin was the most commonly used antibiotic overall, with use in 52% of studies. This was followed by vancomycin (29%) and tobramycin (27%). Beta-lactams (5%), rifampin (1%), and daptomycin (1%) were less common. For $CaSO_4$ beads, vancomycin was the most common antibiotic, being used in 63% of studies. This was followed by tobramycin (51%) and gentamicin (31%).

Table 3 demonstrates the indications for antibiotic bead usage. The most common indication was OM and orthopedic prosthetic infections, making up 72% of the literature. The next most common indication was for use in trauma (9%), usually in the form of contaminated orthopedic wounds. Antibiotic beads have been reported as a means of prophylaxis in high-risk clean or clean-contaminated procedures. These include cases in APR, amputation, and head and neck surgery. The majority of papers on prophylactic use, however, involved orthopedic fractures (60%).

There has been interest in use for prosthetic infections outside of orthopedics (5% of the included literature). The majority of these were for graft infections in vascular surgery (60%). The remaining papers included 1 case of successful treatment of a subcutaneous port infection following gastric banding, treatment of an infected breast implant, and 4 publications regarding infected ventricular assist devices.

While the majority of infections treated involved OM or prosthetics, there have been case reports and a small case series for use in soft tissue infections of the extremities. Three of these used PMMA beads and one paper focused on diabetic foot infections used $CaSO_4$.

Table 2. Level of Evidence and Outcomes by Field of Publication.[a]

	Field					
	Ortho	Vascular Surgery	Plastic Surgery	Wound Care	General Surgery	Other
Level of evidence (%)						
I	1	0	0	0	0	0
II	19	0	0	0	1	1
III	1	0	0	0	0	0
IV	124	11	3	4	2	19
Participants (# treated with beads)						
Greatest number	712	87	104	323	22	41
Median (Q1:Q3)	10 (1:25)	17 (1:35)	7 (2:104)	11 (1:172)	7 (5:22)	2 (1:13)
Conclusions						
Subjective benefit	104	10	3	4	2	15
Benefit statistically sig.	8	0	0	0	1	0
Subjective no benefit	3	0	0	0	0	0
No benefit statistically sig.	8	0	0	0	0	1
Adverse event report	12	1	0	0	0	4
Not reported	10	0	0	0	0	3
Conclusions						
Recommend	117	10	3	4	3	16
Recommend with limitation	14	1	0	0	0	2
Advise against use	6	0	0	0	0	0
No comment	8	0	0	0	0	2
Median follow-up in months (Q1:Q3)	22 (11:37)	20 (13:26)	8 (1:45)	9 (4:36)	15 (6:24)	9.75 (5:18)
Composition of beads						
PMMA	109	9	2	0	3	15
$CaSO_4$	20	2	1	3	0	3
Other/mixed/not defined	15	0	0	1	0	2

Abbreviations: PMMA, polymethylmethacrylate; sig., significant.

[a] Table was composed excluding studies where antibiotic beads was not the variable of interest of the publication. Number of publications at each level of evidence is given. Author conclusion as positive or negative based on either a subjective assessment or a statistical test is given, as well as number of publications reporting an adverse event. Author recommendation regarding use, use in certain circumstances, or against use is given. Median follow-up, composition of beads, and number of participants are given for publications in each field.

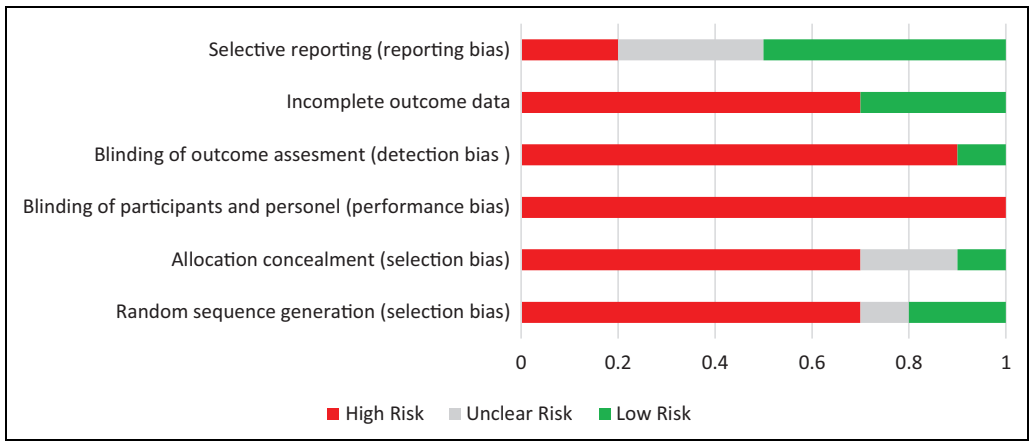

Figure 3. Risk of bias. The proportion of randomized controlled trials being high risk, unclear risk, or low risk of bias in each section of the Cochrane risk of bias categories.

Conflict of Interest

Of included studies, 37% reported the authors having no conflict of interest. Only 4% reported a specific conflict and 59% did not comment at all. Studies not specifying whether there was a conflict were generally published at an earlier date with a median year of publication of 1996 (Q1: 1991, Q3: 2005). The median year of publication was higher for articles reporting a conflict (2012; Q1: 2010, Q3: 2016) and reporting no conflict

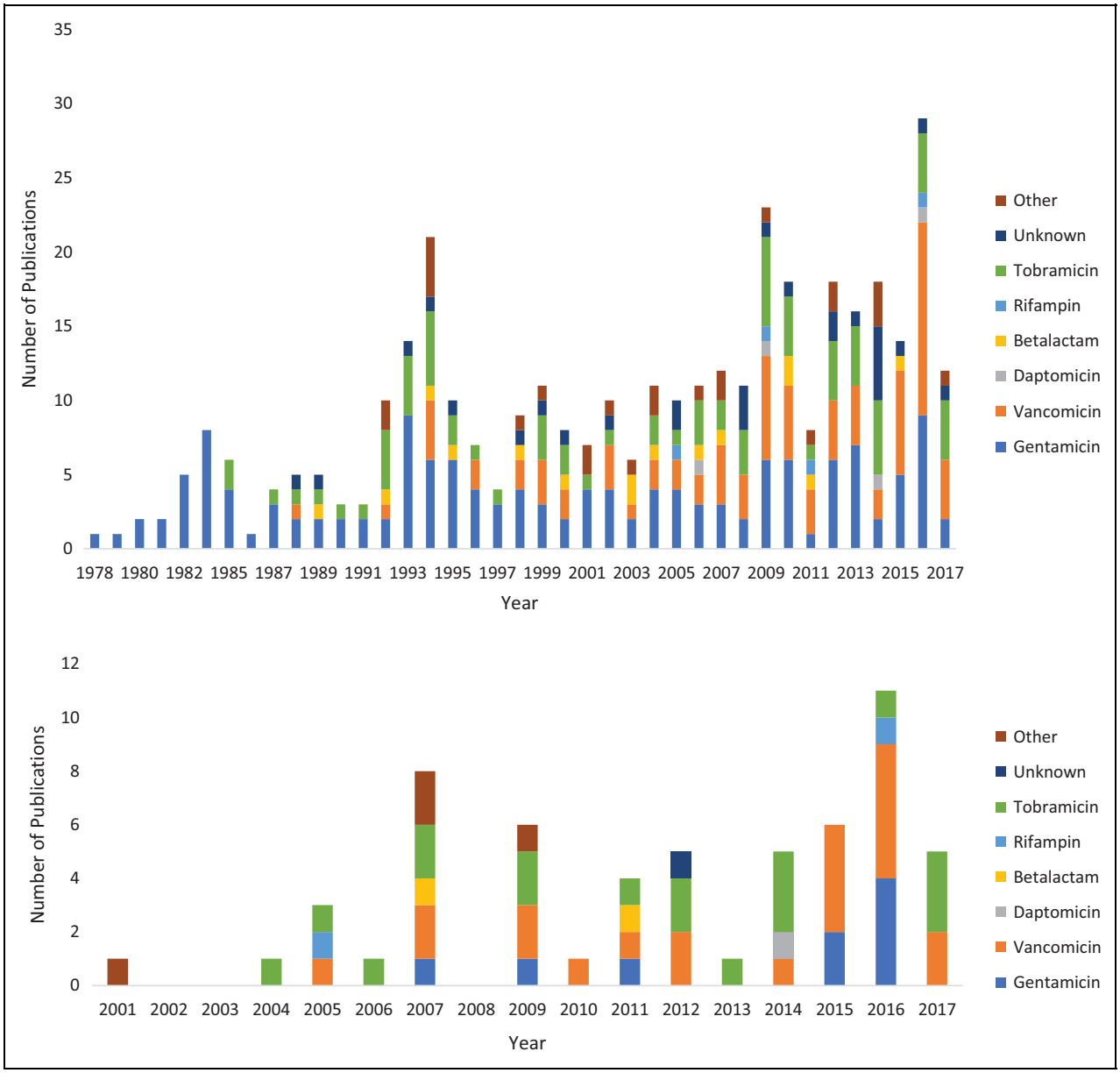

Figure 4. Antibiotic use. Use of different antibiotics are given as the number of papers using that antibiotic within that year. A, Total for all bead compositions. B, Antibiotics used with $CaSO_4$ beads.

(2012; Q1: 2007, Q3: 2014). For articles reporting a conflict of interest, 2 were on PMMA, 4 on $CaSO_4$, 4 on $CaPO_4$, and 2 on both PMMA and $CaSO_4$.

Vascular Surgery

Of the literature identified, 12 articles were specific to vascular surgery and are summarized in Table 4. Four were case reports and 8 were case series. The most common indication was graft infection (10), including both early and late presentation. One case report described a case of fistulization of a PMMA bead chain left at a previous operation, associated with an aortoenteric fistula. One paper described use in mycotic aneurysm repair, with 50% of cases involving reconstruction with prosthetic graft. Only 2 published reports in vascular surgery used $CaSO_4$ as the delivery vehicle.

Vascular graft preservation or in situ reconstruction, with the use of PMMA beads, demonstrated freedom from infection rates of 41% to 87.5%. One series of 6 patients similarly presented graft preservation or in situ reconstruction with the use of $CaSO_4$ beads. While freedom from infection was 100%, follow-up was 7.8 months, which was lower than the PMMA series.

Discussion

The purpose of this review was to provide a broad description of the literature regarding the use of antibiotic beads within

Table 3. Indication for Use by Bead Composition.

	Indication						
Composition	OM	Ortho Prosthetic	Other Prosthetic	Surgical Proph.	Trauma	Soft Tissue	Other
PMMA	101	48	12	7	20	3	17
$CaSO_4$	20	3	2	2	2	1	4
PMMA and $CaSO_4$	4	0	0	0	0	0	0
$CaCO_3$	1	0	0	0	0	0	0
$CaPO_4$	1	0	0	0	0	0	0
Hydroxyapatite	4	0	0	0	0	0	0
Other or not defined	13	3	1	1	4	0	1
Total	144	54	15	10	26	4	22
Percentage	52%	20%	5%	4%	9%	1%	8%

Abbreviations: OM, osteomyelitis; PMMA, polymethylmethacrylate.

[a]Indication for bead use by field is given for all publications. Number of publications for osteomyelitis (OM), orthopedic prosthetic device infection (Ortho Prosthetic), nonorthopedic prosthetic device (other prosthetic), surgical prophylaxis in clean or clean contaminated cases (Surgical Proph.), trauma cases, use in soft tissue, and other indications. Indications are broken down by the composition of beads used in publications. The total number of publications for each indication and the overall percentage of publications that indication makes up are given.

Table 4. Vascular Surgery–Specific Papers.[a]

Paper	Year	Indication	Bead Type	Abx	Syst. Abx	Bead Removal	#	Freedom From Infection	F/u (months)
Bailey et al	1987	AGI	PMMA	G	Yes	No	1	100%	6
Nielsen et al	1991	AGI (11) CGI (6)	PMMA	G	Yes	Yes	17	41%	15
Pasic et al	1992	Mycotic aneurysm	PMMA	G	Yes	No	4	100%	12.5
Banaerts et al	1999	GI Proph WI	PMMA	G	Yes[b]	No (27) Yes (8)	35	GI: 76% Proph: 100% WI: 62%	15
Stone et al	2006	AGI (25) CGI (11)	PMMA	V D T	Yes	Yes	34	87.1%	11
Healy et al	2011	AGI (thoracic)	$CaSO_4$	V T	Yes	No	1	100%	36
Clarke et al[c]	2012	Prophylaxis	PMMA	G	N/A	No	1	N/A	36
Stone et al	2012	AGI (36) CGI (4)	PMMA	G T V	Yes	Yes	40	80.6%	17
Stone et al	2012	AGI (14) CGI (7)	PMMA	G V D T	Yes	Yes	21	N/A	20
Poi et al	2013	AGI (27) CGI (5)[d]	PMMA	G T V F	Yes	Yes	31	87.5%	26
Genovese et al	2016	AGI (5) CGI (1)	$CaSO_4$	G V	Yes	No	6	100%	8
Ali et al	2017	CGI	PMMA	G	Yes	Yes	1	0%	19

Abbreviations: AGI, acute graft infection; CGI, chronic graft infection; F/U, follow-up; GI, graft infection; N/A: not applicable; PMMA, polymethylmethacrylate; WI, wound infections.

[a]Indication for use include graft infection (GI), both acute graft infection (AGI) and chronic graft infection (CGI), mycotic aneurysms, WIs, and as surgical antibiotic prophylaxis (Proph). Antibiotics include gentamicin (G), tobramycin (T), vancomycin (V), daptomycin (D), and fluconazole (F). All studies used systemic antibiotics (Syst. Abx) in addition to local therapy. Number of patients (#) receiving beads in each study is given. The reported rate of freedom from infection is broken down by indication for use when applicable. Average follow-up is given in months.

[b]Yes except for 3 cases of wound infection.

[c]Reports a remote complication from index procedure.

[d]One patient was treated both for an early and then a late graft infection.

surgery. This allowed us to assess the literature in its entirety and analyze the quality of the data, clinical factors such as antibiotic selection, and the clinical indications for use of antibiotic beads. Not all studies primarily focused on antibiotic beads as the primary treatment; however, by including these papers, we were able to produce an unbiased view of how antibiotic beads are used in the published literature.

Interobserver variability was good between reviewers as is reflected by a Cohen κ coefficient of 0.89. One limitation of our search, as is a limitation for most reviews, is the inability to review literature published in other languages. There were 70 articles which had an English abstract otherwise meeting inclusion criteria, however, were excluded as the full text was not available in English. This however may overestimate the amount of data excluded, as we believe some of these papers were later reported in a separate English language publication. We did demonstrate that English language publications are not limited to North America, but contributions came from a wide variety of countries (Table 1).

Quality of Literature

Overall, the quality of evidence is quite low. While positive in nature, the majority of conclusions were subjective (Table 2). This may be influenced by publication bias, however, especially given most studies are observational in nature. With this in mind, there have been observational studies with large sample sizes and reasonable follow-up (Table 2). The small number of RCTs generally had a high risk of bias, had not justified sample size selection, and were underpowered (Figure 3). The period in which there was the greatest interest in RCTs on PMMA antibiotic beads (when Septopal was entering the market), well-constructed, randomized surgical trials were less common. Biodegradable beads, such as $CaSO_4$, are still relatively novel. While lacking in high-quality evidence, the literature is promising that this technology could have a major impact on patient outcomes. As the field further progresses, well-designed RCTs should be conducted to assess for efficacy.

Safety

As with any technology, there are adverse events. The majority of the reports we identified are case studies regarding rare events. These include allergies to components and Redman syndrome from vancomycin beads.[28-30] Mechanical complications have arisen with PMMA bead chains including damage to a bowel or veins in close proximity to the chain and inability to reduce a hip dislocation secondary to bead migration into the acetabulum.[31-33] This is an important factor to note when a decision is made to retain PMMA beads long term, rather than remove them during a subsequent procedure. There have also been reports of increased antibiotic resistance in organisms grown off of PMMA beads which were retained for an extended period of time.[34] These complications with PMMA beads, which remain in situ until they are removed, provide part of the rational for $CaSO_4$ and other biodegradable formulations.

In the literature on $CaSO_4$ beads, we only identified one case series reporting an adverse outcome. Of 15 included patients, 3 had transient elevations in serum calcium levels, with one requiring treatment.[35] This patient was successfully managed with no major complication.[35] He received 40 cc of $CaSO_4$ (Stimulan; Biocomposites, Staffordshire, England), which constitutes 4 packages of the product.[35] It is therefore important for providers to be cognizant of their patient's clinical status and the risk of elevating serum calcium when using high volumes of $CaSO_4$.

There have been reports of infrequent toxicity from gentamicin contained within PMMA beads, including elevated gentamicin level, renal impairment, or decline in hearing function.[23,36-38] Often additional patient factors are present that could explain the outcome, including systemic illness or other sources of gentamicin. Numerous studies have been conducted looking at the serum and fluid antibiotic levels following implantation of both PMMA and $CaSO_4$ antibiotic beads. These have demonstrated tissue levels well above what can be safely attained with IV administration, while serum levels remain below toxic thresholds.[9,39-42] There is an initial peak in serum concentration, followed by a decline over the following days.[40,42] With $CaSO_4$ beads, there is gradual resorption of the beads, with an average time of resorption between 4 and 8 weeks.[15,35] Overall, the number of adverse events reported makes up a very small proportion of the literature, compared to the substantial number of papers demonstrating safety of antibiotic-impregnated beads (Table 2). Caution should be exercised in patients with impaired renal function. In a model by Livio et al, in patients with a creatinine clearance of 30 mL/min, higher doses of tobramycin-impregnated $CaSO_4$ (50 g; 1.3 g tobramycin) can begin to demonstrate toxicity.[41] As renal disease worsens (creatinine clearance < 10), the risk is associated with lower bead quantities (10 g $CaSO_4$; 262 g tobramycin).[41]

Clinical Factors

Aminoglycosides remain the most commonly used antibiotic. Beads are an ideal delivery vehicle for this class of antibiotic as the benefit of broad coverage is attainable while minimizing the systemic toxicity. Our review demonstrates, however, antibiotic choice has broadened allowing more targeted therapy. There have additionally been reports of antifungal use in beads.[43]

Generally, antibiotic beads have been used in combination with systemic antibiotics rather than as a monotherapy. This is likely due to a lack of evidence supporting withholding systemic therapy currently. There have been some small comparisons of treatments with parenteral or combination therapy versus bead monotherapy, which have failed to show a superiority either way.[20,26,44] Case series have reported success with only local antibiotic therapy for orthopedic prosthetic infection, OM, and vascular surgery.[45-47] In a series by Gauland, 86% of

patients with OM of the foot healed with only debridement and use of $CaSO_4$ beads, while the remaining required parenteral antibiotics or higher level amputation.[48] In a study of orthopedic prosthetic infection by Ammon and Stockley, no patients received systemic antibiotics.[49] They found that in 2-stage replacement of infected hip arthroplasty, reasonable results could be achieved with bead monotherapy.[49] They did however believe this strategy could lead to higher reinfection rates in some patients and recommended IV antibiotics should be used in complex patients with multiple ORs and multiresistant organisms.[49] Local monotherapy does offer a means to avoid the systemic toxicity of parenteral antibiotics; however, the exact circumstances where this is appropriate remains unclear. Further research and larger studies are required to explore this issue.

Applications to Vascular Surgery

Antibiotic-impregnated beads are promising in many aspects of vascular surgery; however, there has been limited research. The most extensively studied indication in vascular surgery is the treatment of graft infection. Antibiotic beads already are an important treatment modality in orthopedic prosthetic infections, and as our review demonstrates, the majority of the literature is focused on this topic.[50] This supports the notion that their use in prosthetic-related infections in other fields, where it has been less extensively studied, will be beneficial. Antibiotic beads have also been used with success in cardiac surgery in the treatment of left ventricular assist devices. The largest of these studies included 26 patients, with an infection clearance rate of 65%.[51] The protocol used was similar to reports of treatment of graft infection, with repeat debridement until cultures were negative, prior to definitive closure.[51]

An alternative for local antibiotic therapy in vascular graft infection includes antibiotic-impregnated vascular grafts. Both methods provide a means to deliver local antibiotic therapy.[52,53] Traditional soaking of Dacron grafts with rifampin, however, can lead to rapid elution of the antibiotic, which has prompted investigation of alternative methods of delivery.[52] Antibiotic-impregnated beads have been shown to produce high tissue levels of antibiotic, minimize systemic exposure, and have a long duration of antibiotic elution.[15,39-42] Authors have suggested that there may be improved results with antibiotic-impregnated beads, relative to antibiotic-impregnated grafts, though head-to-head studies have not been completed.[54] Antibiotic beads have the added benefit of being used with autogenous conduit, if available. Alternatively, if autogenous tissue is not used, antibiotic-impregnated grafts can be used in conjunction with antibiotic-impregnated beads.

In treatment of infected grafts with antibiotic beads, rates of freedom from infection are reported up to 87.5%.[55] In the case series by Poi et al and Stone et al, which demonstrated the best freedom from infection rates, debridement and bead exchanges were more frequent (average 2.5) and negative cultures were required prior to definitive closure.[54-56] Genovese et al reported the use of $CaSO_4$ beads with in situ replacement or graft preservation.[57] Due to biodegradability of $CaSO_4$, this may subject patients to fewer operations and allows for beads to be left at the time of final closure. Larger studies with longer follow-up are required for therapy in graft infection.

An important consideration in studies on SSI and specifically vascular graft infection is the reliability of end points.[58] There can be considerable variability in measuring SSI between different criteria and individual interpretation.[58] With vascular graft infection, diagnosis is made based on clinical features; imaging and the diagnosis can be difficult especially with low-grade chronic infections.[59] Recent studies have demonstrated positron emission computed tomography with ^{18}F-fludeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) may be a more reliable means of diagnosis of graft infection.[60,61] Future studies should use strict criteria, set follow-up intervals, and consider newer imaging modalities such as FDG-PET/CT to ensure reliability.

Surgical Site Infection

Prevention of SSI is another indication that warrants investigation. Within orthopedics, the largest study looking at the use of antibiotic-impregnated beads was in open, contaminated fractures by Ostermann et al.[62] In their cohort, they demonstrated a reduction in infection rate when antibiotic-impregnated beads were used in addition to IV antibiotic therapy.[62] Open fractures constitute an extremely high-risk surgical group for infection. While this represents a distinct population from elective procedures, it supports the principle that high-risk patients may benefit from prophylactic antibiotic-impregnated beads in other fields.

In vascular surgery, Benaerts et al described the use of PMMA beads in high-risk patients as a means of prophylaxis for SSI.[47] Using $CaSO_4$ prophylactically provides the added benefit of not requiring removal of beads or leave a foreign body in situ indefinitely. While Benaerts et al did describe the beads can be left in situ, this is not without risk, as described in his series and in the report by Clarke et al.[33] There have been reports of improved healing rates with prophylactic use of $CaSO_4$ beads in transmetatarsal amputations (TMA).[63] In a study by Krause et al, patients underwent fewer revisions following TMA if $CaSO_4$ beads were implanted at the time of surgery.[63] While there have been no studies specific to vascular surgery using $CaSO_4$ beads as a form of antibiotic prophylaxis, it is an area that warrants further investigation for high-risk patients.

Wound Care and Diabetic Foot

A significant portion of the literature on antibiotic beads involves chronic OM. Unlike acute OM, chronic OM often requires surgical debridement with antibiotic beads acting as an important adjunct. Diabetic foot infections, often with coexisting OM, is a pathology often encountered within vascular surgery. There have been numerous case reports of successful therapy using both using PMMA and $CaSO_4$ beads as an adjunct in the management of diabetic foot infections.[64-66]

Again, evidence is limited. In a series conducted by Jogia et al, including only diabetic foot infections, 20 patients treated with $CaSO_4$ beads successfully healed by 5 weeks.[67] Gauland reported the use of $CaSO_4$ in lower extremity OM, mainly involving the foot.[48] They demonstrated resolution in most cases with only debridement and antibiotic-impregnated $CaSO_4$ beads. The success seen in these smaller studies focused on diabetic foot infection, and larger studies of chronic OM highlight this as an important area for further investigation.

Conflicts of Interest

When evaluating any drug or technology, both the quality of the evidence and the objectivity of the investigators play an important role. We found that a large portion of studies did not specify the presence or lack of conflicts. However, studies with appropriate disclosure have more recent mean publication date, in keeping with improved compliance with conflict disclosure over time. There was more conflict of interest disclosure seen within the $CaSO_4$ beads group. This is likely because it is a relatively new technology which is driven by industry. It is important to have large, objective studies moving forward, as $CaSO_4$ beads become a more routine part of practice.

Conclusions

The existing literature regarding antibiotic-impregnated beads demonstrates promising results for the treatment of complex and prosthetic-related infections. With the availability of biodegradable formulations, these indications may begin to expand. One area of interest is use as a prophylactic agent in high-risk patients; however, further study is required. While the results are promising, the literature is mainly observational in nature. Randomized trials that have been conducted are generally at a high risk of bias. More studies are required, especially outside of the orthopedics literature, to better delineate the specific role for antibiotic beads. Within vascular surgery, while evidence is limited, treatment of graft infection, diabetic foot infections, and prophylaxis in high-risk patients are specific areas of interest.

Appendix A

Search strategy for the use of antibiotic-impregnated beads in surgery. This search was used as part of a systematic review currently being prepared for publication.

A. Search of Medline

1. exp antibiotic agent/
2. antibiotic*.ti, ab, kw.
3. antibiotic agent/
4. tobramycin/
5. tobramycin*.ti, ab, kw.
6. gentamicin/
7. gentamicin*.ti, ab, kw.
8. vancomycin/
9. vancomycin*.ti, ab, kw.
10. rifampin/
11. rifampin*.ti, ab, kw.
12. daptomycin/
13. daptomycin*.ti, ab, kw.
14. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. calcium carbonate/
16. calcium sulfate/
17. poly(theyl methacylate)*/
18. (polymethylmethacrylate or PMMA).ti, ab, kw.
19. (calcium sulfate* or CaSO4).ti, ab, kw.
20. (calcium carbonate* or CaCO3) .ti, ab, kw.
21. "plaster of paris".mp.
22. 2 or 3 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. drug implant/
24. biodegradable implant/
25. 23 or 24
26. 22 and 25
27. 1 or 2 or 3 or 14
28. 15 or 16 or 17 or 18 or 19 or 20
29. 27 and 28
30. pellet*.ti, ab, kw.
31. bead*.ti, ab, kw.
32. 30 or 31
33. (2 or 3 or 14) and 32
34. (stimulant or osteoset*).ti, ab, kw.
35. ((impregnated or dissolvable or tobramycin or vancomycin or gendamicin or daptomycin or rifampin or bio-absorbable or absorbable or bioabsorbable or antibiotic* or calcium sulfate or CaSO4 or calcium carbonate or CaCO3 or plaster of paris) adj3 (pellet* or tablet* or bead*)). ti, ab, kw.
36. 26 or 29 or 33 or 34 or 35

B. Search of Embase

1. exp anti-bacterial agents/
2. antibiotic*.ti, ab, kf.
3. anti-bacterial agents/
4. tobramycin/
5. tobramycin*.ti, ab, kf.
6. gentamicins/
7. gentamicin*.ti, ab, kf.
8. vancomycin/
9. vancomycin*.ti, ab, kf.
10. rifampin/
11. rifampin*.ti, ab, kf.
12. daptomycin/
13. daptomycin*.ti, ab, kf.
14. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. calcium carbonate/
16. calcium sulfate/
17. polymethyl methacrylate/
18. (polymethylmethacrylate or PMMA).ti, ab, kf.
19. (calcium sulfate* or CaSO4).ti, ab, kf.
20. (calcium carbonate* or CaCO3) .ti, ab, kf.

21. "plaster of paris".mp.
22. 2 or 3 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. drug implants/
24. absorbable implants/
25. 23 or 24
26. 22 and 25
27. 1 or 2 or 3 or 14
28. 15 or 16 or 17 or 18 or 19 or 20
29. 27 and 28
30. pellet*.ti, ab, kf.
31. bead*.ti, ab, kf.
32. 30 or 31
33. (2 or 3 or 14) and 32
34. (stimulant or osteoset*).ti, ab, kf.
35. ((impregnated or dissolvable or tobramycin or vancomycin or gendamicin or daptomycin or rifampin or bio-absorbable or absorbable or bioabsorbable or antibiotic* or calcium sulfate or CaSO4 or calcium carbonate or CaCO3 or plaster of paris) adj3 (pellet* or tablet* or bead*)). ti, ab, kf.
36. 26 or 29 or 33 or 34 or 35

C. Search of Cochrane Central Register of Controlled Trials

1. MeSH Descriptor: [Anti-Bacterial Agents] explode all trees
2. Antibiotic*
3. MeSh Descriptor: [Gentamicins] explode all trees
4. Gentamicin
5. Mesh Descriptor: [Tobramycin] explode all trees
6. Tobramicin
7. Mesh Descriptor: [Vancomycin] explode all trees
8. Vancomycin
9. Rifampin
10. MeSh descriptor [Rifampin] explode all trees
11. MeSh descriptor: [Daptomycin] explode all trees
12. Daptomycin
13. MeSh descriptor [Drug Implants] explode all trees
14. MeSh descriptor: [Polymethyl Methacrylate] explode all trees
15. PMMA
16. Polymethyl Methacrylate
17. MeSh descriptor [Calcium Sulfate] explode all trees
18. MeSh descriptor [Absorbable Implants] explode all trees
19. MeSH descriptor [Bone Substitutes] explode all trees
20. MeSh Descriptor [Clacium Carbonate] explode all trees
21. CaCO3
22. Calcium Carbonate
23. CaSO4
24. Calcium Sulfate
25. bead
26. pellet
27. Plaster of Paris
28. Stimulan
29. Osteoset
30. {or #1-#12}
31. {or #13-#29}
32. {and #30 -#31}

Appendix B. Prisma Checklist[68]

Section/Topic	#	Checklist Item	Reported on Page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5,6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6,7
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6,7

(continued)

Appendix B. (continued)

Section/Topic	#	Checklist Item	Reported on Page #
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7,8
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7,8
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level) and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	14, 15
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	N/A
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	11/Figure 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see item 16]).	N/A
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, health-care providers, users, and policy makers).	21
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	14/15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research.	20/21
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	21

For more information, visit: www.prisma-statement.org.

Declaration of Conflicting Interests

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