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Supplemental Information

Targeting implant-associated infections:

titanium surface loaded with antimicrobial

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Transparent Methods

Materials and methods

This systematic review was conducted in order to answer the following focused question: *"Do antibiotic-loaded coatings on titanium surface reduce long-term peri-implant infection?"*. This study was performed according to PRISMA statement recommendations for the report of systematic reviews.

Search strategy

An extensive literature search was performed among six electronic databases up to May 9, 2020: PubMed (MEDLINE), Scopus, Web of Science, The Cochrane Library, and Embase. The grey literature was also searched by the System for Information on Grey Literature in Europe (SIGLE) through the OpenGrey. The entire electronic strategy was developed with MeSH terms/entry terms and free terms appropriately combine by boolean operators (OR; AND) and adapted for each database (Please see Supplemental material – Table S1, related Figure 6). The present systematic review and the search strategy was developed with no language and publication time restriction. A manual screening of the reference list of all included studies was performed, preventing any missing articles. Expert authors were contacted for information of ongoing studies and not published data. Additionally, to keep the search strategy up-to-date, alerts were established for each database.

Eligibility criteria

For the systematic review, the studies had to meet the following inclusion criteria: (a) to evaluate antibiotic-loaded coatings on Ti based-material implants; (b) to have a control group with untreated implants or not loaded with antibiotic; (c) to report primary outcomes related to microbial assessment such as biofilm/microbial load (quantitative data) and implant contamination rate. Studies not meeting the inclusion criteria were excluded. Additionally, the studies designated as literature reviews, case reports, case series, in vitro, in silico, descriptive and observational were also excluded. The PICO strategy described below was used:

(P) – Population: humans or animals with Ti based-implants;

(I) – Intervention: surface treatment with antibiotic on Ti implants clearly described;

(C) – Comparison: control (not treated/loaded with antibiotic) implants; and,

(O) – Outcome: biofilm load (bacterial counts, area covered by biofilm, bioluminescence intensity, biovolume or plaque index) and implant contamination rate (bacterial presence).

Study selection

References recorded identified through all databases were imported to Mendeley reference manager (Mendeley Desktop, v1.19.4; Elsevier). Duplicate entries were excluded according to authors' names, the titles of references and year of publication. After elimination of duplicate entries, two reviewers (R. C. C. and B. E. N.) independently screened all titles and abstracts for possible inclusion. In cases of insufficient information provided in papers' abstracts, the full paper was read to evaluate its eligibility. Subsequently, full texts of the remaining papers were analyzed and those that met the inclusion criteria were included. The agreement between the two reviewers regarding the titles and abstracts selection as well as full text was evaluated by Cohen's kappa coefficient (κ). Any disagreements were resolved by discussion and a third author (J. G. S. S.) was consulted to reach a consensus about eligibility.

Data extraction process

Data from the included studies were independently recorded: study features (author(s) and year of publication), animal (species, n value and infection presence), implant information (Ti based-material, surgical site, surface treatment, antibiotic load), time of follow-up, peri-implant infection rate, drug concentration loaded in the surface, in vitro drug release, and microbiological tests characterized by mean and standard deviation. In case of missing data, the corresponding authors were contacted via institutional e-mail and ResearchGate® website. Some papers from the same study were associated under a single report (the most recent publication). For available data only in graphs with no mean and standard deviation exact values, data were extracted using the program WebPlotDigitizer which is considered a reliable tool for data extraction (Burda et al., 2016).

Supplemental Items:

TABLE S1. Search strategy according to different databases, related to the main text and Figure 6.

PubMed (n = 325)	Scopus (n = 522)	Web of Science (n = 413)	Cochrane Library (n = 29)	Embase (n = 229)	OPENGREY (n = 0)
#1 ((((Titanium[MeSH Terms]) OR (Titanium[Title/Abstract])) OR (Titania[Title/Abstract])) AND ((((((Coated materials, biocompatible[MeSH Terms]) OR (coat*[Title/Abstract])) OR (film*[Title/Abstract])) OR (deposit*[Title/Abstract])) OR (surface* treat*[Title/Abstract]) OR (treat* surface*)) **#2** ((((((((((((((((((Antibiotic*[Title/Abstract]) OR (Amoxicillin[Title/Abstract])) OR (Penicillin[Title/Abstract])) OR (Azithromycin[Title/Abstract])) OR (Clarithromycin[Title/Abstract])) OR (Anthracycline*[Title/Abstract])) OR (Gentamicin*[Title/Abstract])) OR (Neomycin[Title/Abstract])) OR (Streptomycin[Title/Abstract])) OR (Streptozocin[Title/Abstract])) OR (Tobramycin[Title/Abstract])) OR (Vancomycin[Title/Abstract])) OR (Ciprofloxacin[Title/Abstract])) OR (Enrofloxacin[Title/Abstract])) OR (Clindamycin[Title/Abstract])) OR (Metronidazole[Title/Abstract])) OR (Doxycycline[Title/Abstract])) OR (Minocycline[Title/Abstract])) OR (Tetracycline[Title/Abstract])))) **#3** ((((((((((((((((((((((((((((((((animal experimentation[MeSH Terms]) OR (models, animal[MeSH Terms])) OR (animals[MeSH Terms])) OR (animal population groups[MeSH Terms])) OR (animals, laboratory[MeSH Terms])) OR (animal*[Title/Abstract])) OR (rat[Title/Abstract])) OR (rats[Title/Abstract])) OR (mice[Title/Abstract])) OR (mouse[Title/Abstract])) OR (murine[Title/Abstract])) OR (rodent*[Title/Abstract])) OR (pig[Title/Abstract])) OR (pigs[Title/Abstract])) OR (rabbit*[Title/Abstract])) OR (dog[Title/Abstract])) OR (dogs[Title/Abstract])) OR (canine[Title/Abstract])) OR (goat*[Title/Abstract])) OR (monkey*[Title/Abstract])) OR (tibia*[Title/Abstract])) OR (radius[Title/Abstract])) OR (subcutaneous*[Title/Abstract])) OR	**#1** (TITLE-ABS KEY ("Titanium") OR TITLE-ABS-KEY ("Titania")) AND ((TITLE-ABS-KEY ("Coated materials, biocompatible") OR TITLE-ABS-KEY (coat*) OR TITLE-ABS-KEY (film*) OR TITLE-ABS-KEY (deposit*) OR TITLE-ABS-KEY ("surface treatment") OR TITLE-ABS-KEY ("surface treatments") OR TITLE-ABS-KEY ("surface treated") OR TITLE-ABS-KEY ("surfaces treated") OR TITLE-ABS-KEY ("treated surface") OR TITLE-ABS-KEY ("treated surfaces")) **#2** (TITLE-ABS KEY (antibiotic*) OR TITLE-ABS-KEY ("Amoxicillin") OR TITLE-ABS-KEY ("Penicillin") OR TITLE-ABS-KEY ("Azithromycin") OR TITLE-ABS-KEY ("Clarithromycin") OR TITLE-ABS-KEY (Anthracycline*) OR TITLE-ABS-KEY (Gentamicin*) OR TITLE-ABS-KEY ("Neomycin") OR TITLE-ABS-KEY ("Streptomycin") OR TITLE-ABS-KEY ("Streptozocin") OR TITLE-ABS-KEY ("Tobramycin") OR TITLE-ABS-KEY ("Vancomycin") OR TITLE-ABS-KEY ("Ciprofloxacin") OR TITLE-ABS-KEY ("Enrofloxacin") OR TITLE-ABS-KEY ("Clindamycin") OR TITLE-ABS-KEY ("Metronidazole") OR TITLE-ABS-KEY ("Doxycycline") OR TITLE-ABS-KEY ("Minocycline") OR TITLE-ABS-KEY ("Tetracycline"))) **#3** (TITLE-ABS-KEY ("animal experimentation") OR TITLE-ABS-KEY ("models, animal") OR TITLE-ABS-KEY ("animals") OR TITLE-ABS-KEY ("animal population groups") OR TITLE-ABS-KEY ("animals, laboratory") OR TITLE-ABS-KEY (animal*) OR TITLE-ABS-KEY ("rat") OR TITLE-ABS-KEY ("rats") OR TITLE-ABS-KEY ("mice") OR TITLE-ABS-KEY ("mouse") OR TITLE-ABS-KEY ("murine") OR TITLE-ABS-KEY (rodent*) OR TITLE-ABS-KEY ("pig") OR TITLE-ABS-KEY ("pigs") OR TITLE-ABS-	**#1** Topic: TS=("Coated materials, biocompatible" OR coat* OR film* OR deposit* OR surface* treat* OR treat* surface*) AND TS=(Antibiotic* OR "Amoxicillin" OR "Penicillin" OR "Azithromycin" OR "Clarithromycin" OR Anthracycline* OR Gentamicin* OR "Neomycin" OR "Streptomycin" OR "Streptozocin" OR "Tobramycin" OR "Vancomycin" OR "Ciprofloxacin" OR "Enrofloxacin" OR "Clindamycin" OR "Metronidazole" OR "Doxycycline" OR "Minocycline" OR "Tetracycline") **#2** Topic: TS=("animal experimentation" OR "models, animal" OR "animals" OR "animal population groups" OR "animals, laboratory" OR animal* OR "rat" OR "rats" OR "mice" OR "mouse" OR "murine" OR rodent* OR pig* OR rabbit* OR dog* OR "canine" OR goat* OR monkey* OR tibia* OR "radius" OR subcutaneous* OR calvaria* OR "calvarium" OR "femur" OR "jaw" OR mandible* OR palat* OR fibula* OR zygoma* OR "in vivo" OR "in situ" OR "clinical" OR "randomized" OR "nonrandomized" OR "non-randomized" OR "trial" OR intervention stud* OR "follow up" OR follow-up* OR patient* OR "human" OR volunteer* OR "quasi-experimental") **Topic: TS=(Titanium OR Titania) AND #1 AND #2**	**#1** MeSH descriptor: [Titanium] explode all trees **#2**(titanium):ti,ab,kw OR (titania):ti,ab,kw **#3 #1 OR #2** **#4** MeSH descriptor: [Coated materials, biocompatible] explode all trees 658 **#5** (coat*):ti,ab,kw OR (film):ti,ab,kw (deposit*):ti,ab,kw OR (surface* treat*):ti,ab,kw (treat* surface*):ti,ab,kw **#6 #4 OR #5** **#7** (antibiotic*):ti,ab,kw OR (amoxicillin):ti,ab,kw (Penicillin):ti,ab,kw OR (Azithromycin):ti,ab,kw (Clarithromycin):ti,ab,kw OR (Anthracycline*):ti,ab,kw (Gentamicin*):ti,ab,kw OR (Neomycin):ti,ab,kw (Streptomycin):ti,ab,kw OR (Streptozocin):ti,ab,kw (Tobramycin):ti,ab,kw OR (Vancomycin):ti,ab,kw (Ciprofloxacin):ti,ab,kw OR (Enrofloxacin):ti,ab,kw (Clindamycin):ti,ab,kw OR (Metronidazole):ti,ab,kw (Doxycycline):ti,ab,kw OR (Minocycline):ti,ab,kw (Tetracycline):ti,ab,kw **#8 #6 AND #7** **#9** MeSH descriptor: [Animal Experimentation] explode all trees **#10** MeSH descriptor: [Models, Animal] explode all trees **#11** MeSH descriptor: [Animal Population Groups] explode all trees	**#1** ('titanium'/exp/mj OR titanium:ti,ab,kw OR titania:ti,ab,kw) **#2** ('biocompatible coated material'/exp/mj OR coat*:ti,ab,kw OR film*:ti,ab,kw OR deposit*:ti,ab,kw OR 'surface* treat*':ti,ab,kw OR 'treat* surface*':ti,ab,kw) AND ('antibiotic agent'/exp/mj OR antibiotic:ti,ab,kw OR amoxicillin:ti,ab,kw OR penicillin:ti,ab,kw OR azithromycin:ti,ab,kw OR clarithromycin:ti,ab,kw OR anthracycline*:ti,ab,kw OR gentamicin*:ti,ab,kw OR neomycin:ti,ab,kw OR streptomycin:ti,ab,kw OR streptozocin:ti,ab,kw OR tobramycin:ti,ab,kw OR vancomycin:ti,ab,kw OR ciprofloxacin:ti,ab,kw OR enrofloxacin:ti,ab,kw OR clindamycin:ti,ab,kw OR metronidazole:ti,ab,kw OR doxycycline:ti,ab,kw OR minocycline:ti,ab,kw OR tetracycline:ti,ab,kw) **#3** ('animal experiment'/exp/mj OR 'animal model'/exp/mj OR 'animal'/exp/mj OR 'experimental animal'/exp/mj OR animal*:ti,ab,kw OR rat:ti,ab,kw OR rats:ti,ab,kw OR mice:ti,ab,kw OR mouse:ti,ab,kw OR murine:ti,ab,kw OR rodent*:ti,ab,kw OR pig:ti,ab,kw OR pigs:ti,ab,kw OR rabbit*:ti,ab,kw OR dog:ti,ab,kw OR dogs:ti,ab,kw OR canine:ti,ab,kw OR goat*:ti,ab,kw OR monkey*:ti,ab,kw OR tibia*:ti,ab,kw OR radius:ti,ab,kw OR subcutaneous*:ti,ab,kw OR	**#1** (Titanium OR Titania) **#2** (Coated materials, biocompatible OR coat* OR film* OR deposit* OR surface* treat*) **#3** (Antibiotic* OR Amoxicillin OR Penicillin OR Azithromycin OR Clarithromycin OR Anthracycline* OR Gentamicin* OR Neomycin OR Streptomycin OR Streptozocin OR Tobramycin OR Vancomycin OR Ciprofloxacin OR Enrofloxacin OR Clindamycin OR Metronidazole OR Doxycycline OR Minocycline OR Tetracycline) **#4** (animal experimentation OR models, animal OR animals OR animal population groups OR animals, laboratory OR animal* OR rat OR rats OR mice OR mouse OR murine OR rodent* OR pig* OR rabbit* OR dog* OR canine OR goat* OR monkey* OR tibia* OR radius OR subcutaneous* OR calvaria* OR calvarium OR femur OR jaw OR mandible* OR palat* OR fibula* OR zygoma* OR in vivo OR in situ OR clinical OR randomized OR nonrandomized OR non-randomized OR trial OR intervention stud* OR follow up OR follow-up* OR patient* OR human OR volunteer* OR quasi-experimental) **#1 AND #2 AND #3 AND #4**

(calvaria*[Title/Abstract])) OR (calvarium[Title/Abstract])) OR (femur[Title/Abstract])) OR (jaw[Title/Abstract])) OR (mandible*[Title/Abstract])) OR (palat*[Title/Abstract])) OR (fibula*[Title/Abstract])) OR (zygoma*[Title/Abstract])) OR (in vivo[Title/Abstract])) OR ((((((((((in situ[Title/Abstract]) OR (clinical[Title/Abstract])) OR (randomized[Title/Abstract])) OR (nonrandomized[Title/Abstract])) OR (non-randomized[Title/Abstract])) OR (trial[Title/Abstract])) OR (intervention stud*[Title/Abstract])) OR (follow up[Title/Abstract])) OR (follow-up*[Title/Abstract])) OR (patient*[Title/Abstract])) OR (human[Title/Abstract])) OR (volunteer*[Title/Abstract])) OR (quasi-experimental[Title/Abstract]))) **#1 AND #2 AND #3**	KEY (rabbit*) OR TITLE-ABS-KEY ("dog") OR TITLE-ABS-KEY ("dogs") OR TITLE-ABS-KEY ("canine") OR TITLE-ABS-KEY (goat*) OR TITLE-ABS-KEY (monkey*) OR TITLE-ABS-KEY (tibia*) OR TITLE-ABS-KEY ("radius") OR TITLE-ABS-KEY (subcutaneous*) OR TITLE-ABS-KEY (calvaria*) OR TITLE-ABS-KEY ("calvarium") OR TITLE-ABS-KEY ("femur") OR TITLE-ABS-KEY ("jaw") OR TITLE-ABS-KEY (mandible*) OR TITLE-ABS-KEY (palat*) OR TITLE-ABS-KEY (fibula*) OR TITLE-ABS-KEY (zygoma*) OR TITLE-ABS-KEY ("in vivo") OR TITLE-ABS-KEY ("in situ") OR TITLE-ABS-KEY ("clinical") OR TITLE-ABS-KEY ("randomized") OR TITLE-ABS-KEY ("nonrandomized") OR TITLE-ABS-KEY ("non-randomized") OR TITLE-ABS-KEY ("trial") OR TITLE-ABS-KEY ("intervention study") OR TITLE-ABS-KEY ("intervention studies") OR TITLE-ABS-KEY ("follow up") OR TITLE-ABS-KEY (follow-up*) OR TITLE-ABS-KEY (patient*) OR TITLE-ABS-KEY ("human") OR TITLE-ABS-KEY (volunteer*) OR TITLE-ABS-KEY ("quasi-experimental")) **#1 AND #2 AND #3**		**#12** MeSH descriptor: [Animals, Laboratory] explode all trees **#13** MeSH descriptor: [Animals] explode all trees **#14** (animal*):ti,ab,kw OR (rat):ti,ab,kw (rats):ti,ab,kw OR (mice):ti,ab,kw OR (mouse):ti,ab,kw OR (murine):ti,ab,kw (rodent*):ti,ab,kw OR (pig):ti,ab,kw OR (pigs):ti,ab,kw OR (rabbit*):ti,ab,kw (dog):ti,ab,kw OR (dogs):ti,ab,kw OR (canine):ti,ab,kw OR (goat*):ti,ab,kw (monkey*):ti,ab,kw OR (tibia*):ti,ab,kw OR (radius):ti,ab,kw OR (subcutaneous*):ti,ab,kw (calvaria*):ti,ab,kw OR (calvarium):ti,ab,kw OR (femur):ti,ab,kw OR (jaw):ti,ab,kw (mandible*):ti,ab,kw OR (palat*):ti,ab,kw OR (fibula*):ti,ab,kw OR (zygoma*):ti,ab,kw (in vivo):ti,ab,kw OR (in situ):ti,ab,kw OR (clinical):ti,ab,kw OR (randomized):ti,ab,kw OR (nonrandomized):ti,ab,kw (non-randomized):ti,ab,kw OR (trial):ti,ab,kw OR (intervention stud*):ti,ab,kw OR (follow up):ti,ab,kw (follow-up*):ti,ab,kw OR (patient*):ti,ab,kw OR (human):ti,ab,kw OR (volunteer*):ti,ab,kw OR (quasi-experimental):ti,ab,kw **#15 #9 OR #10 OR #11 OR #12 OR #13 OR #14**	calvaria*:ti,ab,kw OR calvarium:ti,ab,kw OR femur:ti,ab,kw OR jaw:ti,ab,kw OR mandible*:ti,ab,kw OR palat*:ti,ab,kw OR fibula*:ti,ab,kw OR zygoma*:ti,ab,kw OR 'in vivo':ti,ab,kw OR 'in situ':ti,ab,kw OR clinical:ti,ab,kw OR randomized:ti,ab,kw OR nonrandomized:ti,ab,kw OR 'non randomized':ti,ab,kw OR trial:ti,ab,kw OR 'intervention stud*':ti,ab,kw OR 'follow up':ti,ab,kw OR 'follow up*':ti,ab,kw OR patient*:ti,ab,kw OR human:ti,ab,kw OR volunteer*:ti,ab,kw OR 'quasi experimental':ti,ab,kw) **#1 AND #2 AND #3**	

TABLE S2 - Summary of excluded studies, related to the main text and Figure 6.

Reason for exclusion	Number	Studies
Does not used titanium-based implants	2	Bernthal et al. (2010); Jennings et al. (2015)
Does not evaluate microbial colonization quantitatively on implant surface	18	Vester et al. (2010); Norowski et al. (2011); Stewart et al. (2012); Qu et al. (2014); Walter et al. (2014); Zhang et al. (2014); Nast et al. (2016); Li et al. (2017, 2018, 2020); Schmidmaie et al. (2017); Wan et al. (2017); Sutrisno et al. (2018); Li et al. (2019); Qian et al. (2019); Williams et al. (2019); Sumathra et al. (2020); Yavari et al. (2020).
Microbiological evaluation in bone tissue only	4	Moojen et al. (2009); Yang et al. (2013); Ma et al. (2017); Boot et al. (2020).
Human study without control group	1	Fuchs et al. (2011)
Unavailable full text	2	Liu et al. (2016); Wang et al. (2017)
Other reasons	6	Ren et al. (2014); Liu et al. (2016); Nast et al. (2016a); Nast et al. (2016b); Qu et al. (2016); Zhang et al. (2018).

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