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Association between Guided Antibiotic Treatment and Treatment Duration: A Systematic Review and Meta-analysis

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Abstract

Background and Aim: The distinctive rise of procaclcitonin level during infections and its subsequent decline help to assess response to treatment. Procalcitonin guidance offers personalized antibiotic regimes, particularly beneficial for critically ill patients. We aimed to assess the effect of procalcitonin-guided antibiotic treatment on treatment duration using meta-analysis.

Methods: We searched the Web of Science, Scopus, and PubMed until August 2023. Two coauthors extracted the data using a standardized form, and disagreements were resolved through discussion. Authors' names, publication year, cohort size, country, and treatment duration for control and procalcitonin groups were recorded. We used a random-effects model to calculate the pooled mean differences and Hedges' g with SD estimates, I^2 test to assess heterogeneity, and R and RStudio for statistical analyses and generating forest and funnel plots to evaluate publication biases.

Results: Seventeen studies were included. The procalcitonin group included 2,043 patients; the control group 2,083 patients. The pooled mean difference was −2.34 (95% CI: −3.28; −1.39, p-value < 0.01), indicating that the mean duration of antibiotic treatment was significantly lower among procalcitonin group than the control. Heterogeneity was high among the studies (I^2 = 89%, p-value < 0.01). No significant bias was found among the studies (t = 0.73., p-value = 0.477) according to Egger's test.

Conclusion: This meta-analysis indicates that adopting a procalcitonin-guided approach for treating critically ill sepsis patients reduces the duration of antimicrobial treatment. Further research is required to identify optimal procalcitonin cutoffs for discontinuing antibiotics among diverse patients, including critically ill surgical cases and immunocompromised individuals.

Key words: *procalcitonin, antibacterial agents, patients, antimicrobial drug resistance.*

Introduction

Standard guidelines emphasize promptly initiating broad-spectrum antibiotics treatment for individuals diagnosed with sepsis or septic shock. This guidance is founded by observational research and highlights a

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appropriate antibiotic treatment and high short-term mortality rates (1, 2). However, extended use of antimicrobial treatments precedes potential adverse consequences, added expenses, and contributes to the development and spread of bacterial resistance (3-5).

Accurately determining the resolution of infections, especially in critically ill patients, remains a complex challenge due to the limited specificity of common clinical indicators and standard laboratory tests. To tackle this issue, scientists have endeavored to identify a dependable biological marker capable of effectively confirming resolution of bacterial infections and helping the decision-making to discontinue antibiotic treatment. Amid these biomarkers, procalcitonin has attracted much attention (3-8).

Many studies have provided evidence that procalcitonin levels rise in response to bacterial infections and decline with recovery (9-11). Consequently, procalcitonin has emerged as a potential marker signifying infection resolution. Thus, researchers have hypothesized that implementing a procalcitonin-guided algorithm could be a valuable tool for guiding the cessation of antibiotic treatment (4, 11-18). Many trials were undertaken to explore the potential advantages of measuring serum procalcitonin levels as a tool for determining the appropriate duration of antibiotic treatment in subjects affected by various types of infections (4, 16, 17).

In 2016, a comprehensive clinical trial assessed the effectiveness and safety of incorporating procalcitonin-guided antibiotic treatment in critically ill patients with sepsis (19, 20). Importantly, the study documented a significantly low mortality rate for the procalcitonin-guided group in comparison to the standard-of-care group. Hence, we aimed to evaluate the effect of procalcitonin-guided antibiotic treatment on antibiotic treatment duration using meta-analysis.

METHODS AND MATERIALS:

We conducted this study according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), 2020 (21).

1.1. Literature search

Electronic databases, including Web of Science, Scopus, and PubMed, were systematically searched from the beginning until August 2023. The search included a combination of relevant medical subject headings and relevant keywords: (“procalcitonin” OR “PCT” OR “Pro-CT”) AND (“antibiotic therapy” OR “guided therapy” OR “antibiotics”). The relevant MeSH terms and some interchanged words (for example, therapy/treatment) were included in the search strategy.

1.2. Eligibility criteria

We determined our eligibility criteria based on the PICO framework: (P) Population: Septic patients. (I) Intervention: antibiotic treatment according to procalcitonin guidance. (C) Comparison: duration of antibiotic therapy. (O) Outcome: difference in the duration of antibiotic treatment. The exclusion criteria were absence of rigid randomization, lack of individual data, non-randomized studies, and non-

English papers.

1.3. Data extraction and outcome measures

Two independent authors extracted the data using a standardized form. Discordances were resolved through discussion with a third party. The standardized form included authors' name, year of publication, total number of participants (cohort size), and country of the study along with mean duration of antibiotic therapy for both control and procalcitonin group, with their standard deviation (SD) and total number.

1.4. Statistical analyses and data synthesis

The pooled mean difference was calculated using a random-effects model and Hedges' g along with SD estimation. For assessing the heterogeneity of the included studies, the I^2 (I square) test was used. The Mantel–Haenszel method and random-effects model were used for pooling the effect sizes, and SD was consequently calculated. For testing the overall significance of the random model, *z*-test was performed. Potential publication bias was graphically assessed by creating funnel plots for each of the groups and performing Egger's test. R (R Foundation for Statistical Computing, Vienna, Austria) and RStudio (RStudio, Inc., Boston, MA) were used for statistical analysis and generating forest and funnel plots.

RESULTS:

By systematic searching the literature, we obtained 4,033 studies, primarily. After removing the duplicates (847), 3,186 studies were screened by their titles and abstracts. Finally, 81 studies were included for full-text retrieval and evaluation. Based on our inclusion and exclusion criteria, 17 studies (22-38) were included in our final meta-analysis. The PRISMA flow diagram of the included studies is presented in Figure 1. Also, study characteristics are summarized in Table 1.

Table 1. Detailed Characteristics of the Included Studies

Name	**Year**	**Country**	**N**	**procalcitonin**			**Control**		
				n	***Mean***	***SD***	***n***	***Mean***	***SD***
Velly et al. (23)	2023	France	451	76	4.64	6.8	67	4.94	6.81
Gavazzi et al. (35)	2022	France	107	26	8.35	3.92	57	10	3.04
Mazlan et al. (29)	2021	Malaysia	85	43	10.28	2.68	42	11.52	3.06
Labro et al. (31)	2021	France	159	81	11.5	22.4	78	8	14.7
Kyriazopoulou et al. (32)	2021	Greece	266	125	5.7	1.5	131	10.7	6
Liu et al. (22)	2017	China	98	49	7.74	0.61	49	10.22	0.71
Oliveira et al. (27)	2013	Brazil	94	49	8.1	3.7	45	7.2	3.5

Long et al. (30)	2011	China	156	77	4.75	2.07	79	7	2.84
Bouadma et al. (38)	2010	France	621	307	10.3	7.7	314	13.3	7.6
Stolz et al. (24)	2009	Switzerland	101	51	10.5	5.2	50	15.75	7.25
Hochreiter et al. (34)	2009	Germany	110	57	5.9	1.7	53	7.9	0.5
Schroeder et al. (26)	2009	Germany	27	14	6.6	1.1	13	8.3	0.7
Schuetz et al. (25)	2009	Switzerland	1359	671	5.7	2.02	688	8.7	2.1
Kristoffersen et al. (33)	2008	Denmark	210	103	5.15	1.76	107	6.65	2.28
Nobre et al. (28)	2007	Switzerland	79	39	12.25	10.14	40	13.5	11.49
Christ-Crain et al. (36)	2006	Switzerland	302	151	5.8	5.3	151	12.9	6.5
Christ-Crain et al. (37)	2004	Switzerland	243	124	10.9	3.6	119	12.8	5.5

A total of 2,043 patients received antibiotic treatment in the procalcitonin group and 2,083 patients received antibiotic treatment in the control group. The mean difference of the duration of antibiotic treatment ranged from −0.30 to −7.10 among the included studies.

Based on the results of our meta-analysis, the pooled mean difference based on the random-effects model was −2.34 (95% CI: −3.28; −1.39, *p-value < 0.01*). This indicates that the mean duration of antibiotic therapy was significantly lower among procalcitonin group compared to the control groups. The heterogeneity was high among the included studies (I^2 = 89%, *p-value < 0.01*).

The publication bias was assessed graphically by a funnel plot (Figure 2) and Egger's test. Although some asymmetry was observed on the funnel plot,

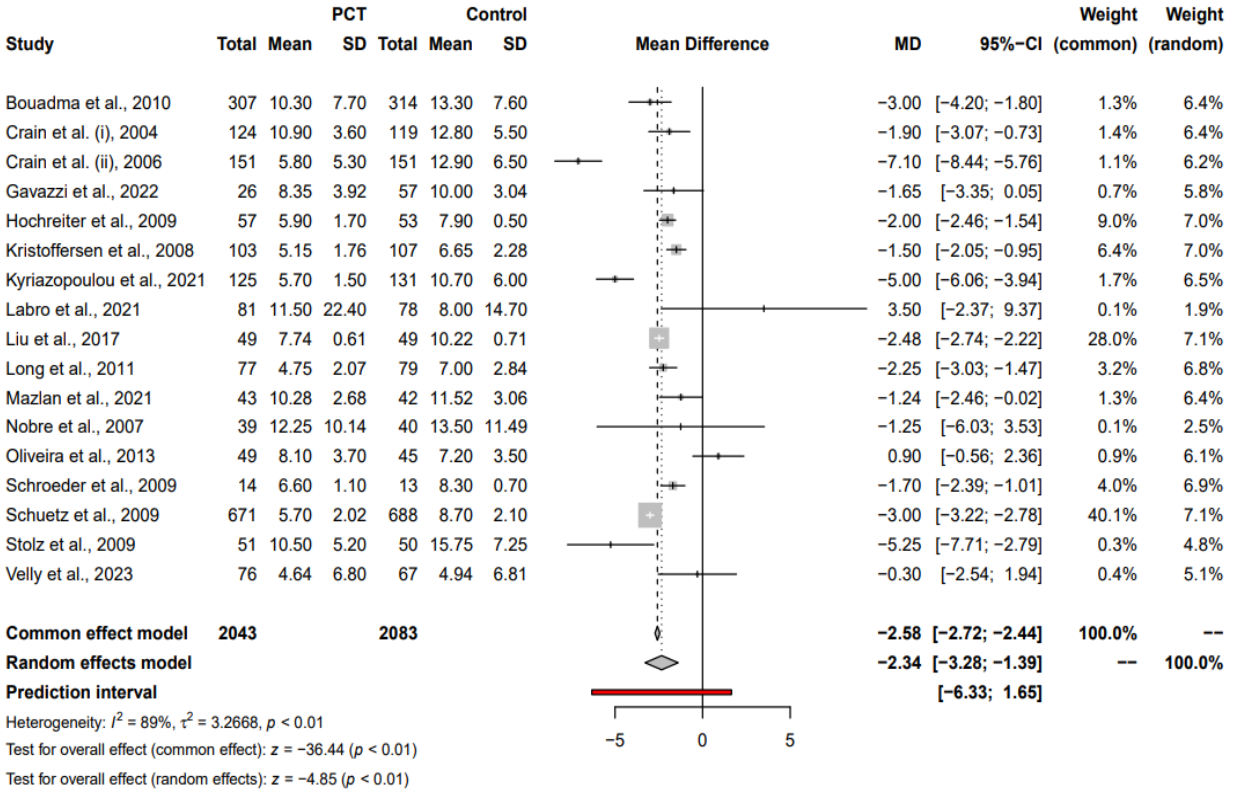

Figure 2. Forest Plot of the Pooled Mean Difference in procalcitonin versus Control Group

Egger's test showed no significant bias among the studies (*t = 0.73., p-value = 0.477*). The funnel plot is shown in Figure 3.

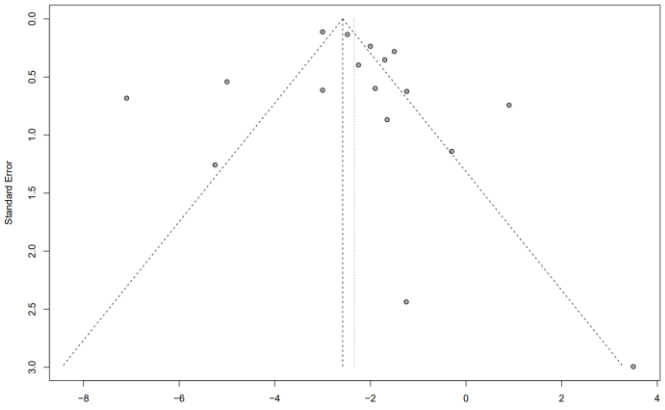

Figure 3. Funnel Plot Showing the Publication Bias among the Studies

DISCUSSION:

Procalcitonin is as a biomarker specific for bacterial infections that is used in different clinical settings including primary care, emergency department, and intensive care. Procalcitonin measurement aids in diagnosing sepsis and can guide and monitor antibiotic treatment. A significant association between subjects infected with sepsis and high serum levels of procalcitonin has convinced the researchers to investigate its wider applications. This meta-analysis confirms that using a procalcitonin-guided approach to determine the cessation of antibiotic treatment reduces the duration of treatment with antibacterial agents. However, the study could not investigate any influence on the length of hospital

stay.

Procalcitonin-guided treatment algorithms supplement the conventional clinical methods for guiding the duration of antibiotic treatment under different clinical scenarios, including patients with sepsis or septic shock. Clinicians often hesitate to curtail the duration of antibiotic treatment in patients with sepsis or septic shock because of a perceived potential risk that could theoretically elevate mortality rates. The “stop antibiotics on procalcitonin guidance study” (SAPS) conducted with 1546 critically ill patients reported that incorporating procalcitonin guidance decreased the median duration of antibiotic treatment and, surprisingly and notably, reduced the mortality rates. Thus, meta-analyses offer a rational framework for assessing the potential impact on survival outcomes by using a procalcitonin-guided algorithm to determine the discontinuation of antibiotics in critically ill patients with sepsis or septic shock. However, meta-analyses have contrarily produced conflicting outcomes on this subject.

Authors of two separate meta-analyses concluded that using procalcitonin-guided approaches for managing antibiotics in critically ill patients did not significantly reduce the mortality rates (39, 40). Unlike our study, these meta-analyses incorporated a randomized controlled trial that investigated the use of procalcitonin for determining both the start and duration of antibiotic treatment in critically ill patients with a high probability of sepsis, as indicated by procalcitonin levels. This study excluded patients displaying clear signs of infection (41). Similarly, we excluded the randomized controlled trial conducted by Heilmann et al. (42) from our analysis due to their examination of procalcitonin as a diagnostic tool for initiating antibiotic treatment in critically ill patients suspected of having sepsis.

In two other meta-analyses, no disparities in 28-day mortality rates were found when the authors evaluated all the trials identified in their comprehensive systematic search. However, upon narrowing the focus to the assessment of procalcitonin-guided cessation of antibiotic treatment, a statistically significant reduction in mortality rates was observed (43, 44). Furthermore, an examination of data from eight randomized controlled trials revealed that in studies designed for antibiotic discontinuation, the short-term mortality rate of the intervention group was notably lower than that of the control group (45). Notably, this specific meta-analysis excluded the study which explored the role of procalcitonin and C-reactive protein in guiding antibiotic treatment of patients with sepsis (26). We highlight that these three meta-analyses did not incorporate the study conducted by Bouadma et al. (38) in their analysis for both initiation and discontinuation of antibiotics.

Our study does not provide insight into the underlying mechanisms that might elucidate the notable survival advantage linked to a reduced antibiotic exposure. Several clinical investigations have documented a significant decrease in

mortality rates with antimicrobial streamlining in patients with sepsis (46, 47). Additionally, extended administration of empirical antibiotics in patients suspected of nosocomial infections has been correlated with unfavorable outcomes. A study examining two antimicrobial stewardship strategies found that hospital mortality risk was increased when empirical antibiotic duration exceeded seven days compared to a reference duration of one to three days. Different meta-analyses consistently revealed a noteworthy reduction in antibiotic usage, with reductions ranging from −1.19 days to −2.68 days. Our findings similarly confirmed an average reduction of approximately two days (9, 29, 42, 43). This shorter duration of antibiotic treatment in critically ill patients with sepsis is significant clinically, ecologically, and economically. Nevertheless, noting that the absolute duration of antibiotic treatment in the procalcitonin arm of these trials remained relatively lengthy suggests that antibiotic prescription practices could potentially be further improved (48-50).

Our study has many limitations. Firstly, the absence of a universally accepted algorithm for discontinuing antibiotic treatment of critically ill patients with sepsis is noteworthy. Furthermore, the studies included in our meta-analysis used varying cutoff values for procalcitonin levels. This heterogeneity among the trials is a significant limitation shared by all the meta-analyses because different trials assessed diverse procalcitonin-guidance strategies, algorithms, or measurement techniques. Additionally, we highlight that some studies lacked data on 28-day mortality.

CONCLUSIONS:

In summary, our meta-analysis presents compelling evidence that implementing a procalcitonin-guided strategy among critically ill patients with sepsis significantly decreases the duration of antimicrobial treatment. Further exploration is needed to determine the optimal procalcitonin cutoff point for discontinuing antibiotics and its relevance among diverse patient populations, including critically ill surgery patients and immunocompromised patients. Nevertheless, we strongly recommend integrating procalcitonin guidance into antimicrobial stewardship initiatives to aid in determining the appropriate duration of antibiotic treatment of patients with sepsis.

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Figure legends:

Figure 1. PRISMA flow diagram of the systematic search and study selection.

Figure 2. Forest Plot of the Pooled Mean Difference in procalcitonin versus Control Group

Figure 3. Funnel Plot Showing the Publication Bias among the Studies

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes

Section and Topic	Item #	Checklist item	Reported (Yes/No)
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes.
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes.
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes.
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes.
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes.
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes.
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes.
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes.
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes.
OTHER			
Funding	11	Specify the primary source of funding for the review.	
Registration	12	Provide the register name and registration number.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Lines 1 and 2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Provided separately
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	57–69
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	73–74
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	87–92
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	81
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	81–86
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	81–86
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	94–98
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	94–98
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	94–98
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of	104–105

Section and Topic	Item #	Checklist item	Location where item is reported
		automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	100–107
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	106–107
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	106–107
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	104
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	109–117
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of	20a	For each synthesis, briefly summarise the characteristics	

Section and Topic	Item #	Checklist item	Location where item is reported
syntheses		and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

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