



Published in final edited form as:

J Infect Public Health. 2018 ; 11(4): 455–462. doi:10.1016/j.jiph.2017.09.024.

Repeat gram-negative hospital-acquired infections and antibiotic susceptibility: A systematic review

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Abstract

Repeat HAIs among frequently hospitalized patients may be contributing to the high rates of antibiotic resistance seen in gram-negative bacteria (GNB) in hospital settings. This systematic review examines the state of the literature assessing the association between repeat GNB HAIs and changes in antibiotic susceptibility patterns. A systematic search of English language published literature was conducted to identify studies in peer-reviewed journals from 2000 to 2015. Studies must have assessed drug resistance in repeat GNB infections longitudinally at the patient level. Two researchers independently reviewed search results for papers meeting inclusion criteria and extracted data. Risk of bias was assessed using a modified quality assessment tool based on the Checklist for Measuring Study Quality and the Quality Assessment Checklist for Cases Series. From 3385 articles identified in the search, seven met inclusion criteria. Five reported lower antibiotic susceptibility in repeated infections, one found a change but did not specify in which direction, and one reported no change. All studies were of low to average quality. Despite the dearth of studies examining repeat GNB infections, evidence suggests that repeat infections result in lower antibiotic susceptibility among hospitalized patients. Larger scale studies with strong methodology are warranted.

Keywords

Repeat infection; Hospital-acquired infection; Gram-negative bacteria; Antimicrobial susceptibility

Introduction

Over 648,000 patients in US hospitals develop hospital-associated infections (HAIs), with approximately 75,000 of those patients dying due to related complications each year [1].

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Competing interests

None declared.

Ethical approval

Not required.

Almost one-third of all HAIs and 60% of HAIs in intensive care units are caused by gram-negative bacteria (GNB) [1–4]. GNB are becoming increasingly resistant to available antibiotics as widespread antibiotic use has surged globally [5,6]. Chronically ill patients who are repeatedly hospitalized are at greater risk for GNB infections and may in fact contract multiple infections throughout their hospitalization history [7–9].

Repeated HAIs caused by the same organism among frequently hospitalized patients may be contributing to the high rates of antibiotic resistance seen in GNB in hospital settings. Multiple infections likely result from a combination of general host risk factors, inappropriate or prolonged antibiotic treatment, and organism persistence factors such as biofilms and persister cells [10–15]. When exposed to the hospital environment multiple times, it is possible that these persistence factors put patients at greater risk of acquiring or developing a drug-resistant infection. Furthermore, individuals with chronic pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) are particularly prone to the development of antimicrobial resistance with continued bacterial colonization [16,17]. The current literature has extensively described the effect of prior antibiotic use on antibiotic resistance and the use of antibiotic stewardship in reducing resistance [18,19]. However, less is known about the role of previous GNB HAIs on antibiotic susceptibility in subsequent HAIs with the same organism. This systematic review examines the state of the literature assessing the association between repeat GNB HAIs and changes in antibiotic susceptibility patterns.

Methods

To be included in the systematic review, articles must have met the following criteria: (1) published in a peer-reviewed journal between January 1, 2000 and December 31, 2015, (2) primary research written in English, (3) have an abstract and full text available, (4) assess drug resistance in repeat GNB infections longitudinally as a primary or secondary outcome. The search start date of January 2000 was chosen to account for the increasing incidence of drug resistant GNB infections beginning in the early 2000s in the United States [5,20]. Articles assessing the effect of treatment on an infection were excluded as well as studies that were done solely in CF or COPD patients, who have increased risk of repeat colonization and infection. Other exclusions included single patient case studies, articles only studying community-acquired infections, articles focused on salmonella and other food-borne diseases, and articles without data at the individual patient level. Conference presentations and dissertations were also excluded.

The search was conducted using the PubMed and Embase databases with a combination of Medical Subject Headings (MeSH) and keywords. The search terms are shown in Table 1. A professional medical librarian was consulted to review and refine search terms and strategy. Relevant articles were extracted and stored using reference management software (EndNote X7; Thomas Reuters) and duplicates were deleted.

Two reviewers, both with an MPH and doctoral candidacy in epidemiology, independently screened titles and abstracts of articles to determine whether the inclusion criteria were met. Full-text articles were then reviewed by the same two reviewers and reference lists of those

articles were searched for potentially relevant publications. Few disagreements regarding eligibility assessments of the articles between the two reviewers were discussed and resolved by joint consensus.

The following data were extracted from the final articles: publication journal, publication year, country in which the study was conducted, research questions, study time frame, sample, study design, analytic approach, organism, determination and definition of repeat infection, and findings related to antibiotic susceptibility changes. The quality of the selected studies was assessed by both reviewers using a modified quality assessment tool based on the Checklist for Measuring Study Quality and the Quality Assessment Checklist for Case Series [21,22] which were developed for observational case series and case-control study designs, respectively. Questions relating to study randomization, blinding and interventional aspects were removed as they did not apply to the studies in this review. Items were scored as “Yes” (Y), “No” (N), “Partial” (P), “Unclear/unable to determine” (U) and “Not applicable” (NA) and weighted equally. The overall quality of the studies was based on the following scores: Good (G): at least 80% of criteria met; average (A): between 50% and 80% of criteria met; and poor (P): 50% of criteria met.

Results

The search yielded 3385 potential articles (Fig. 1). After applying the inclusion and exclusion criteria, 29 articles were selected for full text review. Seven final articles were identified after the exclusion process for the following reasons: (1) no assessment of antibiotic susceptibility changes over time (n = 12), (2) only conducted among patients with CF or COPD who have differential and higher risk of repeat infection (n = 1) (3) conference abstracts (n = 6), (4) no comparison of antibiotic susceptibility changes within the same individual (n = 1), and (5) primarily focused on community-acquired infections (n = 2).

Characteristics of included studies

The included studies were conducted in Australia, Canada, Israel, South Korea, Switzerland, Taiwan, and the United States (Table 2) [23–29]. All of them were cohort studies, with three being prospective and the other four retrospective. The inclusion and exclusion criteria varied across studies; all but one study included only patients with confirmed repeat infection or colonization [24–29]. The Patel et al. study included only patients 18 years while the Ram et al., St. Denis et al., Yang et al., and Yum et al. studies included only adults >18 years [23,25,27–29]. The Qi et al. and Reinhardt et al. studies did not provide details on the study patients' age [24,26]. Two studies recruited patients from multiple hospitals [23,27]. Six of the seven studies included 41 patients with repeat infections; Ram et al. included data from 271 patients but not all had infections caused by gram-negative bacteria [23–29]. Patel et al. screened over 56,000 patients but reported 39 patients with drug-resistant isolates collected on different dates [23]. One study included only two patients [26]. Organisms examined included exclusively *Burkholderia cepacia complex* (n = 1), exclusively *Pseudomonas aeruginosa* (n = 2), exclusively *Acinetobacter baumannii* (n = 1), exclusively *Klebsiella pneumoniae* (n = 1), all GNB (n = 1), and all bacteria (n = 1).

The definition of the timing of repeat infections differed among the studies. One study defined repeat infection as positive culture sat least 30 days apart, another defined recurrence as occurring at least one year apart, and another as at least two months after the completion of antibiotic therapy [24,28,29]. The St. Denis et al. required two or more positive cultures within 12 months [27]. Three studies did not describe a specific time difference between positive isolates [23,25,26].

One study did not report any type of statistical analyses [28]. Of the other six studies, one used correlations and three used bivariate analyses including χ^2 tests, Fisher Exact tests and Student's t-tests [23,26,27,29]. Two studies used logistic regression to calculate odds ratios [24,25]. The six studies did not use the statistical tests to evaluate change in drug resistance between repeat infections.

Antibiotic susceptibility changes in repeat infections

Six of the seven studies found that the GNB causing repeat infections had reduced antibiotic susceptibility patterns as compared to initial or early infections [23–27]. The Yang et al. study found no change in susceptibility for *K. pneumoniae* liver abscesses and the Yum et al. study did not specify the direction of antibiotic susceptibility changes among the 30% of repeat cases that had a change [29].

Quality assessment

Based on the quality assessment tool, five studies were of average quality and two were poor quality (Table 3). None of the studies had adequate power to detect statistically significant differences, reported loss-to-follow up rates, or adjusted for different follow up times in their analyses or discussions. Only one publication examined potential confounders [25].

Discussion

Hospitalized patients who experience repeat HAIs are understudied yet represent an increasingly important group in the effort to slow the spread of antibiotic resistance. Repeat infections are due to an infection with a new strain of an organism, an infection with the same organism due to environmental or bacterial persistence, or from a relapse of the prior infection-causing organism. All three may result in patients developing future drug resistant infections. Several studies have examined whether repeat infections represent re-infections with a different strain or relapse of prior infections [29–31]. Yet surprisingly, only a few studies have examined repeat infections of GNB, despite the devastating outcomes associated with these organisms in hospital settings [32–34]. A study published in 1999 and not included in this review, examined repeat gram-negative bacteremia among patients to identify relapsed infections versus reinfections with a different strain of the same organism [35]. However, in this study, 60% of the infections were community-acquired. There is a need to assess repeat GNB infections within hospital settings since there is a greater chance of acquiring a drug-resistant GNB infection in hospitals [36–38].

In this review, we found only seven published studies that examined changes in antibiotic susceptibility in GNB among patients with repeat infections since 2000. Greater drug resistance was generally found in patients with higher numbers of repeat infections,

suggesting that if initial infections were contained, subsequent resistant infections could be prevented. Studies focused on *Staphylococcus aureus* have found that patients with initial sensitive infections who are at higher risk of subsequent resistant infections can be identified [39,40]. Unfortunately, we were not able to identify common risk factors for recurrence of GNB infections within the studies in this review.

The quality of the literature included in this review limits our ability to determine with strong evidence that there is an increase in antibiotic resistance in repeat hospital-acquired GNB infections. The studies, which were of average to low quality, did not have adequate sample sizes or statistical power to evaluate if there was a change in antibiotic susceptibility in repeat GNB infections. They also differed in what they considered a repeat infection, for example whether the later infection occurred 30 days or a year after the initial infection. Additionally, all but one of the studies provided only descriptions of occurrence of repeat infections as opposed to risk of occurrence of repeat infections with and without drug resistance. Hence, the published literature, while suggestive, does not strongly substantiate the association between repeat infections and antibiotic susceptibility.

Future research should not only assess whether there is increased drug resistance in repeat GNB infection, but also what patient and hospital risk factors are associated with repeat infections and drug resistance. Patients who are older and/or have chronic illnesses are likely at disproportionately higher risk of repeat HAI. For example, the Patel et al. paper examined risk factors for acquiring a multidrug resistant infection or multiple infections with resistance to multiple drugs and found that patients with more admissions, stay in a long-term care facility, higher number of days in an intensive care unit, and higher number of days with a catheter had a greater risk of having repeat infections with drug resistance [23]. Identifying risk factors that put patients at greater risk for a repeat infection as well greater risk of a drug-resistant infection will help in focusing infection prevention and care resources.

Future studies should identify larger samples of hospitalized patients with repeat infections by using electronic medical records or large national data sets that would contain long-term infection history in order to ensure sufficient statistical power to identify associations. In addition, future research can assess whether an association between repeat GNB infections and lower antibiotic susceptibility is due primarily to prior antibiotic exposure in order to guide antibiotic stewardship and other infection control initiatives.

This systematic review has certain limitations. The inclusion criteria for the review were relatively narrow; nevertheless, studies that met our inclusion criteria were heterogeneous in-patient samples and in their definitions of repeat infections so it was not possible to do a meta-analysis. We may have missed articles in the literature search due to other variations in terminology. Finally, there is the possibility of publication bias, as we did not include conference abstracts, dissertations, or other grey literature. Articles not published in English or available through library services were also excluded.

Conclusions

Despite the limitations, this review suggests that repeat GNB infections contribute to drug resistance in hospitals and highlights the need for further research. Repeat GNB HAIs most likely affect patients with multiple hospitalizations, the so called “frequent flyers”, or those who have extensively long hospital stays. Repeat GNB infections in these chronically ill patients, particularly older patients, can result in increased complications, higher mortality, increased hospital and patient costs, and greater risk of future infections [41]. At a time when drug resistance among GNB is increasingly prevalent, reducing repeat infections may lead to fewer drug resistant infections in hospitals and improve outcomes in patients.

Acknowledgments

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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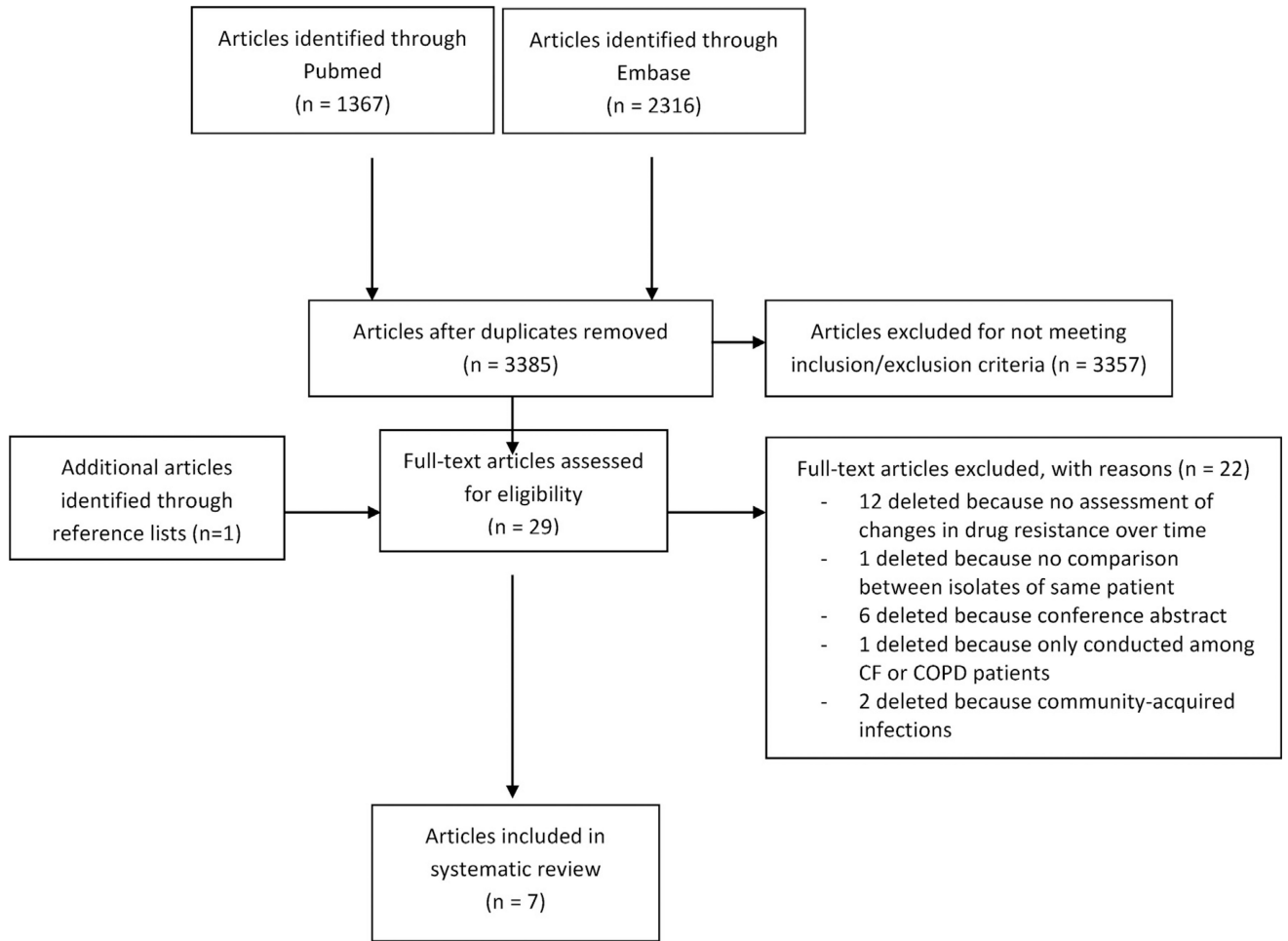


Fig. 1.
Flow diagram of article search.

Table 1

Literature search terms.

Database	Date of search	Search terms	Number of results
Pubmed	08/05/2016	((("Gram-Negative Bacteria"[MeSH] and "Drug Resistance"[MeSH] AND "Bacterial Infections"[MeSH] AND ("Recurrence"[MeSH] or repeat or previous or chronic or persistent or persistence or longitudinal))) AND ("2000/01/01"[PDat]: "2015/12/31"[PDat]) AND Humans[MeSH] AND English[lang])	1367
Embase	08/05/2016	'drug resistance'/exp OR 'drug resistance' AND ('gram negative bacteria'/exp OR 'gram negative bacteria') AND ('recurrence'/exp OR 'recurrence' OR 'repeat' OR 'persistent' OR 'longitudinal' OR 'chronic') AND [humans]/lim AND [english]/lim AND [2000–2015]/py	2316

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Table 2

Summary of key characteristics of publications included in the systematic review.

Authors	Year	Setting	Inclusion/exclusion criteria	Sample size	Study design	Analytic approach	Examined organisms	Definition of repeat infection	Findings on change in antibiotic susceptibility
Patel et al. [23]	2012	New York City	Patients 18 years of age or younger who were hospitalized from January 1, 2006, to December 31, 2008	56,235	Retrospective cohort	Descriptive, χ^2 , Fisher Exact tests, t-tests	All GNB	isolation of more than 1 GNB collected over more than 1 date	39/56,235 patients had additive DR, including 10/39 with additive DR from cultures across 2 or more admissions, and 6/39 patients who developed later infection/colonization with MDR GNB
Qi et al. [24]	2009	Chicago, IL	Patients with multiple positive clinical cultures of <i>A. baumannii</i>	41	Retrospective cohort	Descriptive, logistic regression	<i>A. baumannii</i>	2 clinical isolations of <i>A. baumannii</i> separated by at least 30 days	Patients with initial carbapenem-resistant isolates had more closely related isolates obtained for subsequent cultures than patients with non-carbapenem-resistant isolates, whereas patients with initial susceptible isolates frequently lost the initial strain and developed colonization/infection with a resistant and genetically distinct <i>A. baumannii</i> .
Ram et al. [25]	2012	Petah-Tikva, Israel	All consecutive hospitalized patients with fever of unknown origin, clinically documented infection or microbiologically documented infection after intensive chemotherapy or hematopoietic cell transplantation	271	Prospective cohort	χ^2 or Fisher Exact test, multivariate logistic regression for mortality	All bacteria	infections developing during or after antibiotic treatment	Higher antibiotic susceptibilities were observed with initial infections compared with subsequent infections in patients with GNB infection
Reinhardt et al. [26]	2007	Geneva, Switzerland	Intubated patients in surgical and medical intensive care units with respiratory tract colonization by <i>P. aeruginosa</i>	2	Prospective cohort	Ratios, correlations	<i>Pseudomonas aeruginosa</i>	Colonization of <i>P. aeruginosa</i> despite multiple antibiotic treatments	Resistant isolates appeared 6–10 days after treatment, persistent colonization was due to mutations in original strain and not cross-colonization with new <i>P. aeruginosa</i>
St. Denis et al. [27]	2007	Ten Canadian and two Australian sites	Confirmed diagnosis of cystic fibrosis, > 12 years old, able to spontaneously produce sputum, and chronically infected with MDR Bcc, <i>P. aeruginosa</i> , <i>Sten. maltophilia</i> , or <i>Ach. xylosoxidans</i> bacteria	36	Prospective cohort	Paired t tests, Fisher Exact test	<i>Burkholderia cepacia</i> complex	2 sputum cultures within the past 12 months	Bcc. isolates retrieved during exacerbations were less sensitive to meropenem, ciprofloxacin, chloramphenicol, piperacillin, and tobramycin compared to isolates retrieved during clinically stable periods.
Yang et al. [28]	2009	Taiwan	Patients with repeat KLA at least 1 year after the onset of the first KLA	6	Retrospective cohort	Descriptive	<i>Klebsiella pneumoniae</i>	KLA occurring at least 1 year after the onset of the first KLA	No change in antibiotic resistance in repeat infection
Yum et al. [29]	2014	Seoul, Korea	Patients with 2 or more different periods of recurrences	18	Retrospective cohort	T-tests, one-way analysis of variance	<i>Pseudomonas aeruginosa</i>	Occurrence after complete treatment of previous pneumonia without evidence of extrapulmonary source of infection	7/24 repeat cases had different antibiotic phenotype

Abbreviations: KLA: *Klebsiella*-infected liver abscesses; MDR: multi-drug resistant organisms.

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Table 3

Risk of bias assessment for included studies.

	Patel	Qi	Ram	Reinhardt	St. Denis	Yang	Yum
First author							
Study question	Y	Y	Y	Y	Y	P	Y
1. Is the hypothesis/aim/objective of the study stated in the abstract, introduction, or methods section?							
Study population	Y	Y	Y	Y	Y	Y	Y
2. Are the characteristics of the patients included in the study clearly described? (number, gender, age, etiology).							
3. Was the case series collected in more than one center? (If the study is multicenter, the question should be answered 'yes'.)	Y	N	N	N	Y	N	N
Comparability of subjects/samples							
4. Are the eligibility criteria explicit and appropriate? (Inclusion and exclusion criteria should be stated.)	Y	P	Y	Y	Y	Y	N
5. Were data collected prospectively?	N	N	Y	Y	Y	N	N
6. Were patients recruited consecutively?	Y	U	Y	U	U	U	U
7. Did patients enter the study at a similar point in the disease?	Y	U	Y	N	N	N	U
8. Were the subjects recruited during the same period of time?	Y	Y	Y	Y	Y	Y	Y
9. Was there loss to follow-up reported?	N	N	N	NA	N	N	N
Outcome measurement (change in antibiotic susceptibility)							
10. Are outcomes (primary and secondary) clearly defined in the introduction or methodology section?	Y	Y	Y	Y	Y	N	Y
11. Did the authors use accurate (standard, valid, reliable) objective methods to measure the outcomes? (Systematic, repeatable methods of case finding and appropriate lab definitions used?)	Y	Y	Y	Y	Y	P	Y
12. Was there assessment of outcome before and after the study?	Y	Y	Y	Y	Y	Y	Y
13. Was the length of follow-up clearly described/reported?	Y	Y	N	Y	Y	P	N
Statistical analysis							
14. Were the statistical tests used to assess the primary outcomes appropriate? (No if no statistical tests)	Y	Y	Y	N	Y	N	Y
15. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the primary outcome measurements except where the probability value is less than 0.001? (NA if Q14 is N)	Y	Y	Y	NA	Y	NA	N
16. Does the study provide estimates of the random variability in the data for the primary outcomes? (e.g. standard error, standard deviation, confidence intervals)	Y	Y	Y	NA	Y	N	N
17. Was there a discussion/assessment of possible confounders?	N	N	Y	N	N	N	N
Results							
18. Are the main findings of the study clearly described?	Y	Y	Y	Y	Y	Y	Y
19. Do the analyses adjust for different lengths of follow-up of patients? If follow-up is differential between groups, was this controlled for in the design or analysis?	N	N	N	N	N	N	N
20. Do the study's findings respond to research objectives/question(s)?	Y	Y	Y	Y	Y	Y	Y

First author	Patel	Qi	Ram	Reinhardt	St. Denis	Yang	Yum
21. If any of the results of the study were based on "data dredging", was this made clear? Discussion/conclusion	NA	N	Y	Y	Y	N	N
22. Are the conclusions supported by results?	Y	Y	Y	Y	Y	Y	Y
23. Are the limitations of the study taken into consideration?	Y	Y	Y	Y	P	N	N
24. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? (No if no mention of power)	N	N	N	N	N	N	N
Total	18	14	19	15	17	7	10
Yes	5	7	5	5	5	12	12
No	0	1	0	0	1	3	0
Unclear/unable to determine	0	2	0	2	1	1	2
Quality rating ^a	A	A	A	A	A	P	P

^aThe studies rated with respect to quality criteria as follows: good (G): at least 80% of criteria met; average (A): between 50% and 80% of criteria met; poor (P): 50% of criteria met.