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Prophylactic antibiotics for anterior nasal packing in Emergency Department: A Systematic Review and Meta- Analysis of Clinically-Significant Infections

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Keywords: Anterior epistaxis; anterior nasal packing; prophylactic; antibiotics; complications

Prophylactic Antibiotics for Anterior Nasal Packing in the Emergency Department: A Systematic Review and Meta-Analysis of Clinically Significant Infection

ABSTRACT

Background: Patients presenting to emergency departments with spontaneous anterior epistaxis may undergo anterior nasal packing and sometimes receive systemic prophylactic antibiotics. There has not been sufficient evidence to support or refute this practice. The main objective of this study was to compare the likelihood of clinically significant infection (CSI) between patients with or without prophylactic antibiotics for anterior nasal packing due to spontaneous epistaxis.

Methods: We performed a meta-analysis of the literature to assess whether prophylactic antibiotics prevented CSI among patients with anterior nasal packing by searching PubMed, Embase, and Scopus databases for original articles. We also looked at the secondary outcome of non-infectious complications. We reported the outcomes using random effect models. Human studies in English, randomized control trials, quasi-randomized trials, clinical trials, retrospective studies, and case series were included. We excluded studies involving patients undergoing otolaryngologic surgeries. Statistical heterogeneity was examined using the DerSimonian and Laird Q test and I^2 statistic.

Results: A total of 281 articles were identified. Of these, 5 articles met inclusion criteria, with 383 patients receiving anterior nasal packing. One hundred sixty (42%) patients did not receive prophylactic antibiotics while 223 (58%) received antibiotics. The proportion of CSI in the pooled cohort was 0.8% (95% CI 0.2-1.9), resulting in a number needed to treat (NNT) to prevent one infection of 571. The rate of non-infectious complications associated with epistaxis was 20% (95% CI 10-32).

Conclusions: This meta-analysis suggests that prescribing prophylactic antibiotics for anterior nasal packing may not be necessary due to the low proportion of CSIs across heterogenous patient populations. Further high-quality randomized trials are needed to support this finding.

Keywords: Anterior epistaxis; anterior nasal packing; prophylactic antibiotics

INTRODUCTION

Epistaxis occurred in 1 per 200 emergency department (ED) visits in the United States from 1992 to 2001 [1] and 90% of those occurrences were anterior bleeding from Kiesselbach plexus, which is located just inside the nares[2]. Short-term nasal packing—often used to treat epistaxis if conservative local measures (pressure, silver nitrate cauterization) do not stop bleeding—can be left in place for a few days to control bleeding [2]. Frequently, patients with nasal packing are prescribed prophylactic antibiotics due to providers' concern for potential toxic shock syndrome, sinusitis, or otitis media [3]. Although toxic shock syndrome is rare in patients with anterior nasal packing and has only been reported in case studies [4,5], it is an important consequence because it carries the risk of mortality even in healthy patients [6].

The Centers for Disease Control and Prevention reports that up to 30% of antibiotics prescriptions from physicians' offices and ED are unnecessary [7]. The rise of antibiotic resistance has been attributed to inappropriate prescription [8] and widespread use [9,10] of antibiotics. The economic burden caused by antibiotic-resistant bacterial illness is severe, estimated to be $55 billions of dollars in the United States in 2000 [11]. The cost of antibiotic resistance is projected to be $100 trillion worldwide by the year 2050 [10] . Van Der Velden et al. suggest that improving physicians' awareness about appropriate antibiotic use is an effective way to reduce unnecessary antibiotic prescriptions [12].

Although there has not been strong evidence to support the use of prophylactic antibiotics among patients with anterior nasal packing [13], Murano et al. reported up to 54% of emergency providers prescribed prophylactic antibiotics [14]. This practice is not without risk, as giving patients unnecessary antibiotics could lead to rising rates of antibiotic resistance and patient harm from adverse drug effects [9,10].

Besides Cohn's narrative review, which included small studies and did not involve ED patients [13], there has been no comprehensive review of this topic in ED patients. We aimed to assess whether prophylactic antibiotics prevent clinically significant infections (CSI) in patients undergoing anterior nasal packing. To achieve this goal, we performed a systematic review and meta-analysis involving a large cohort of patients who had spontaneous epistaxis.

METHOD

Search Strategy

Our study conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and performed in accordance with best practice guidelines [15]. We performed searches, up to August 23, 2019, in PubMed, Scopus, and Embase databases. For PubMed search, the Medical Subject Headings (MeSH) terms "epistaxis" AND "anti-bacterial agents" used, while keyword terms "epistaxis" AND "antibiotics" AND "nasal packing" used for Scopus and Embase searches. Our detailed search strategy is provided in Appendix 1. We included articles that were in English and evaluated human studies including patients receiving prophylactic antibiotics in the setting of spontaneous epistaxis and short-term anterior nasal packing. We included prospective randomized control trials, quasi-randomized control trials, clinical trials, retrospective studies, and case series. We excluded studies involving children younger than 18 years. We also excluded articles studying antibiotics and any nasal packing after otolaryngologic surgeries or packing for posterior epistaxis. This study registered with PROSPERO, an international database of prospectively registered systematic reviews.

Outcome

The primary outcome was defined as CSIs such as sinusitis, otitis media, abscess or cellulitis of face or nares, and toxic shock syndrome. We defined the secondary outcome as non-infectious complications from nasal packing, such as recurrence of bleeding, otalgia, and facial pain. We reported the outcomes using random effect models.

Study Selection and Data Extraction

Two authors independently screened each study's title and abstract against the inclusion criteria. Each study needed both authors' agreements to be included for full-text review. Discrepancies were adjudicated by discussion between authors. We reviewed full texts of selected studies and determined suitability for inclusion. We reviewed the full text version of the articles for potential references. Primary and secondary outcomes and complications data were extracted by one author and confirmed by a senior author using double data entry.

Quality Assessment

We utilized the Newcastle-Ottawa scale (NOS) to assess the methodological quality and risk of bias of the included non-randomized studies and the Cochrane Collaboration's tool for assessing randomized control trials [16,17]. The 9-point NOS assessed 3 domains: 1) selection of the cohort, 2) comparability of the groups, and 3) quality of outcome. High-quality studies have a score ≥ 7, whereas moderate- and low-quality studies have scores of 4–6 and ≤ 3, respectively [17]. Two authors independently performed the NOS. We resolved any disagreements between the 2 authors through discussion and consensus after reviewing NOS ratings of previously examined studies [17].

Statistical Analysis

We used weighted Cohen's kappa score to assess inter-raters' agreement on study quality, based on poor agreement (≤ 0.2), fair agreement (0.21- 0.40), moderate agreement (0.41-0.60), good agreement (0.61-0.80), or a very good agreement (0.81- 1.00).

We performed meta-analyses when 3 or more studies reported any of the primary outcomes. We pooled together incidences of CSIs or non-infectious complications from all studies. We reported the outcomes as random effect models. Absolute risk reduction (ARR) was calculated as the difference between the pooled incidence of CSIs among patients with or without prophylactic antibiotics.

We examined the statistical heterogeneity using the DerSimonian and Laird Q test and I^2 statistic. We performed meta-analyses using the MedCalc software (MedCalc Statistical Software version 19, Ostend, Belgium).

RESULTS

The PRISMA flowchart in appendix 2 demonstrates our search results. The search yielded 281 citations, but after title and abstract review, we identified 15 articles for full-text critical appraisal. We identified and included 5 articles in our meta-analysis (Table 1).

A Cohen's kappa of 0.78 (95% confidence interval [CI] 0.45-1.0) indicated good agreement between investigators. There was significant heterogeneity based on study type

(prospective observational vs. retrospective), setting (ED vs inpatient), and practice variability (emergency vs otolaryngologist). Among the 5 relevant studies, there were 2 studies involving patients in the ED and 3 with otolaryngologic inpatients (Table 2).

There was a total of 383 patients from 5 studies (Table 2). There were 160 patients (42%) who were not given prophylactic antibiotics while 223 patients (58%) received prophylactic antibiotics. The proportion of CSI among patients who had anterior nasal packing was 0.8% (95% CI 0.16 – 1.97) (Figure 1).

A total of 304 patients were included in the meta-analysis for non-infectious complications from anterior nasal packing. The Murano et al.[14] study did not report complications as an outcome, so it was not included in this meta-analysis. The 4 studies that reported non-infectious complications did not specify the numbers of non-infectious complications between patients receiving or not receiving antibiotics, so we were unable to assess the odds ratios of non-infectious complications between the 2 groups. The proportion of non-infectious complications was 20% (95% CI 10.3 – 32.9) (Figure 2). The most common complications were re-bleeding (22/304) [18], otalgia (14/304) [19], positive bacterial growth on nasal swab (9/304) [20] prompting patients to continue antibiotics after discharge, and sinonasal symptoms (8/304) [21]. The authors of the study that included the 9 patients who continued antibiotics did not specify whether the patients had received prophylactic antibiotics. Nonetheless, they considered those patients as not having any CSI.

Two studies reported the rates of complications between patients receiving anterior nasal packing with or without prophylactic antibiotics [19,21]. Therefore, we did not perform meta-analysis assessing the odds ratios of complications between those receiving or not receiving prophylactic antibiotics, as there were insufficient data for such analysis (Table 3)

We calculated the NNT to prevent CSI in our pooled patients (Appendix 3). The Absolute Risk of developing CSI for patients receiving antibiotics was 0.45% while the Absolute Risk for developing CSI for patients without antibiotics was 0.625% (Appendix 3). The ARR between the groups with or without prophylactic antibiotics was 0.00175 (95% CI 0.02 - 5.57) (Appendix 3). The NNT was 571. The likelihood of developing CSI in those not receiving antibiotics was non-significant when compared to those receiving antibiotics (Odds Ratio 1.4, 95% CI 0.9 - 22, p=0.99).

DISCUSSION

We planned to perform a meta-analysis evaluating the risk of infection among patients with epistaxis receiving antibiotics versus those not receiving antibiotics in the setting of anterior packing. One study reported the presence of CSI; the rest of the studies explicitly reported no infection. As a result, we performed a post hoc proportional meta-analysis to assess the random-effect incidence of infection in the pooled patient population. Our analysis' result by random effects showed that the proportion of patients who experienced CSI after undergoing anterior nasal packing was only 0.8% of the pooled cohort. A higher proportion (20%) had non-infectious complications associated with epistaxis.

Widespread use of antibiotics is the leading cause of antibiotic resistance [9,10] and the Centers for Disease Control and Prevention reports that up to 30% of antibiotics prescriptions from physicians' offices and ED are unnecessary [7]. Besides bacterial resistance, in general, antibiotic-related *clostridium difficile* infection is also an important risk of antibiotic use [22]. One patient among 80 patients undergoing anterior or posterior nasal packing and received prophylactic antibiotics reported *clostridium difficile* infection [23]. While the study did not report the severity of this patient's *clostridium difficile* infection, it is difficult to draw conclusion based on a single case.

Cohn's 2015 study suggests that antibiotics for anterior nasal packing should be reserved for patients with immunosuppression [13], although there has not been strong data to support this suggestion. There is also one case report of toxic shock syndrome in a patient who had bone marrow transplant for acute myeloid leukemia and received anterior nasal packing.[5] We were unable to examine the effect of immunosuppression on risk of infection after nasal packing, as only one study within our meta-analysis examined patient immunocompetency[14].

Due to lack of clear consensus or guidelines, the practice of prescribing antibiotics for patients with anterior nasal packing varies. Up to 37% of otolaryngologist in a United Kingdom study in 2005 reported giving prophylactic antibiotics with anterior nasal packing [24]. Two retrospective, single-center studies in the United States reported incidence of prophylactic antibiotic prescription in EDs as 61% in 2001 [18] and 46% between 2012 and 2016 [14]. Although these reflect a trend toward decreased prescription of antibiotics, almost 50% of patients with anterior nasal packing still received prophylactic antibiotics in the 2019 study [14]. Future

investigators should attempt to conduct multicenter studies to obtain larger sample sizes of patients with higher CSI incidence and to assess variations in patterns and types of prophylactic antibiotic prescribing

LIMITATIONS

There are several limitations, which prevent us from drawing definitive conclusions regarding prophylactic antibiotics and CSI in patients with anterior nasal packing. All of the included studies were either observational or retrospective. The pooled incidences of CSI and the NNT in our study should be interpreted with caution because of heterogeneity among types of studies, patient settings, and practices of emergency physicians and otolaryngologists. While there was some heterogeneity in patient populations, by pooling the incidences of examined outcomes, our study suggests low incidence of CSI despite the different settings and practices. Two of the studies were retrospective and may not have accounted for patients who had CSIs but did not return to the study facilities. While the I-square statistics of the proportion of clinically significant infection suggested homogeneity, it was likely because all the reported CSI came from one single study. There was large heterogeneity of non-infectious complications between studies, as each study observed different types of complication. Despite the meta-analysis of the 5 studies, the overall number of patients was not large. The pattern of antibiotics prescription did not represent the practice variations of prophylactic antibiotics prescription; thus, further multicenter study is warranted. Two of the studies were retrospective and may not have accounted for recall bias or patients who had CSIs but did not return to the study facilities. We were not able to determine if any studies used topical antibiotic prior or during the insertion of anterior nasal packing. The exact type of anterior nasal packing was not included in the study analysis and we are unable to categorize different types of anterior nasal packing.

CONCLUSION

This meta-analysis showed that the proportion of CSI among patients with epistaxis and anterior nasal packing is low at less than 1% in our pooled patient population. However, the proportion of non-infectious complications after anterior nasal packing was higher at 20%. This

study suggests that prophylactic antibiotics prescription for anterior nasal packing may not be necessary in all patients; however, further study specifically in the Emergency Department setting is warranted.

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Table 1. Assessment of Study Quality Using the Newcastle-Ottawa Scale.

References	Newcastle-Ottawa Scale			
	Selection (4)	**Comparability (2)**	**Outcome (3)**	**Total Score (9)**
Germann 2004 [18]	1	1	1	3
Biswas 2009 [20]	3	0	1	4
Pepper 2012 [19]	3	1	2	6
Biggs 2013 [21]	3	1	1	5
Murano 2019 [14]	4	1	1	6

Table 2. Summary of articles included in the meta-analysis.

	Germann 2004[18]	**Biswas 2009**[19]	**Pepper 2012**[17]	**Biggs 2013**[20]	**Murano 2019**[13]
Study Design	Retrospective	Prospective observation	Prospective Before-After	Retrospective	Retrospective
Settings	Emergency Department	Otolaryngology Inpatient	Otolaryngology Inpatient	Otolaryngology Inpatient	Emergency Department
Control, N	Anterior nasal packing with antibiotics, N= 49	Anterior nasal packing with antibiotics, N=13	Anterior nasal packing with antibiotics, N=78	Anterior nasal packing with antibiotics, N=38	Anterior nasal packing with antibiotics, N=45
Interventions, N	Anterior nasal packing without antibiotics, N=31	Anterior nasal packing without antibiotics, N=15	Anterior nasal packing without antibiotics, N=71	Anterior nasal packing without antibiotics, N=19	Anterior nasal packing without antibiotics, N=24
Length of packing (hours)	Not reported	48-72	24-36	48	Not reported
Outcome Definitions	Clinical signs of infection (no specific symptoms listed); any complications	Clinical sign of infection (fever, nasal discharge, facial pain, headache). Bacterial growth from packing,	Clinical signs of infection (symptoms of sinusitis, otitis media, purulent nasal discharge; facial pain, otalgia)	Clinical signs of infection (no specific symptoms listed); any complications	Clinical signs of infection (purulent nasal drainage, fever, erythema, abscess or cellulitis of the mid-face or nares)
Methods for Outcome Assessment	Chart reviews	Nasal swabbing for microbiology, nasal endoscopy	Nasal endoscopy; otoscopy;paper questionnaire	Telephone survey	Chart reviews
Length of follow-up	Not reported	7 days	At hospital discharge	6 weeks	Not reported
Any Reported infection	None	None	None	2 sinusitis (one for each group)	None
Any Complications	22 re-bleeding (unclear about each arm)	9 received further antibiotics (unclear about each group)	14 otalgia (7 for each group)	8 (nasal discharge, crusting, pain) (unclear about each group)	Not reported

Table 3. Summary of Prophylactic Antibiotics Prescribed For Patients With Epistaxis And Anterior Packing

	Germann 2004 [18]	**Biswas 2009** [20]	**Pepper 2012** [19]	**Biggs 2013** [21]	**Murano 2019** [14]
Name of antibiotics	Not reported	Amoxicillin + clavulanic acid	Amoxicillin + clavulanic acid	Amoxicillin + clavulanic acid	Not reported
Dosage	Not reported	Not reported	625 mg three times daily	625 mg three times daily	Not reported
Duration	Not reported	Up to 3 days	5 days	5 days	Not reported

Appendix 1. Detail of search strategy for each of the 3 databases.

PubMed

"Epistaxis"[Mesh] AND "Anti-Bacterial Agents"[Mesh] AND (full text[sb] AND Humans[Mesh] AND English[lang])

Scopus

#3 TITLE-ABS-KEY (epistaxis AND antibiotics AND nasal AND packing)

#2 TITLE-ABS-KEY (epistaxis AND antibiotics AND packing)

#1 TITLE-ABS-KEY (epistaxis AND antibiotics)

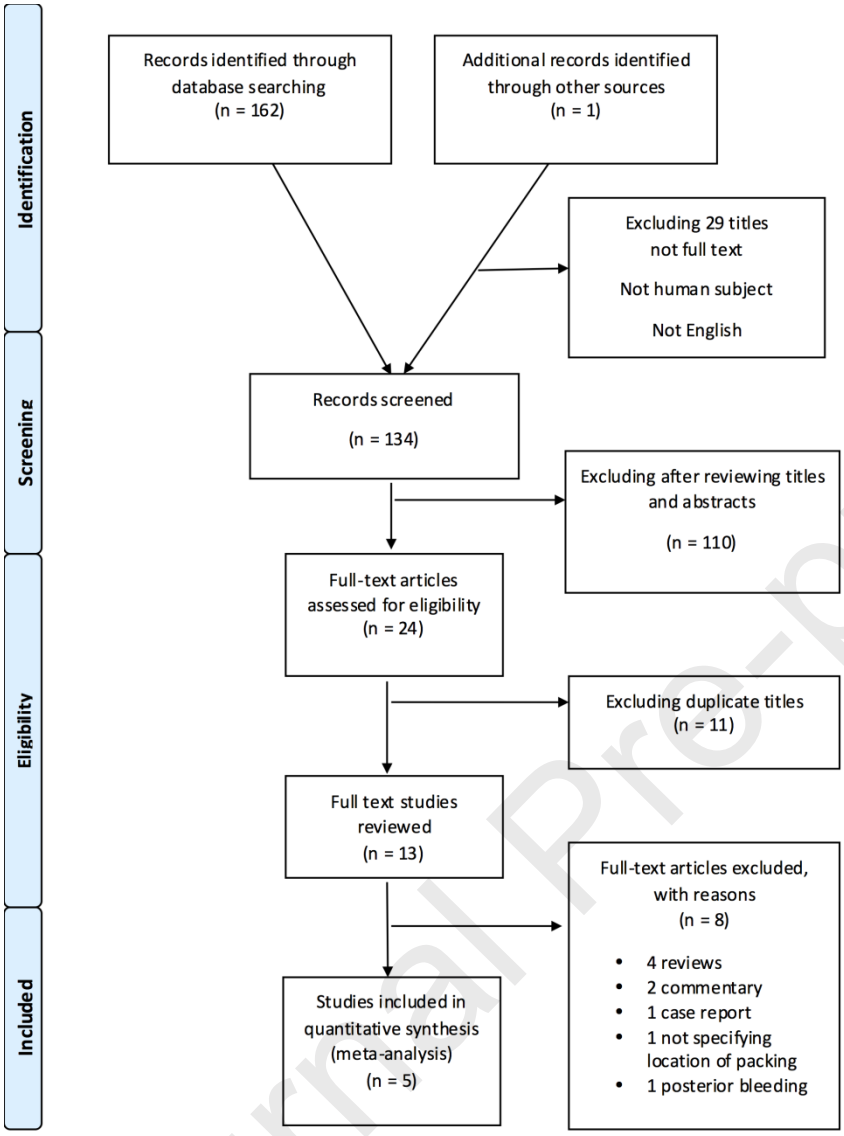
EMBASE

#3 epistaxis:ti,ab,kw AND antibiotics:ti,ab,kw AND 'packing':ti,ab,kw

#2 epistaxis:ti,ab,kw AND antibiotics:ti,ab,kw AND 'nasal packing':ti,ab,kw

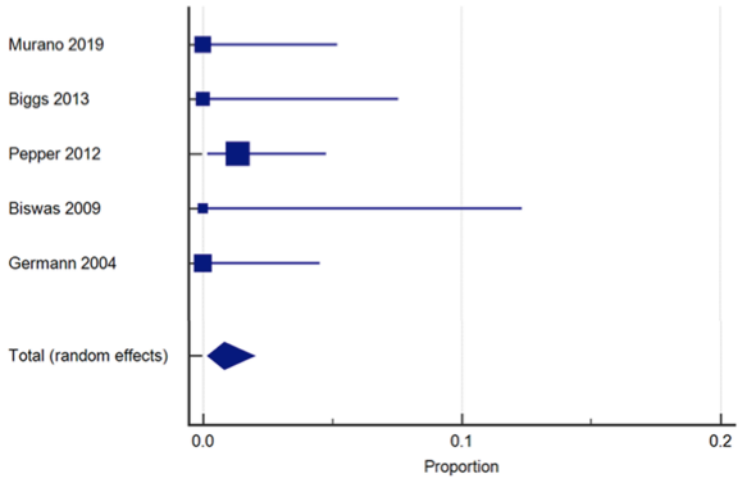
#1 epistaxis:ti,ab,kw AND antibiotics:ti,ab,kw

Appendix 2



Appendix 3. Calculation of the number needed to treat (NNT) for pooled patients with anterior nasal packing with or without prophylactic antibiotics.

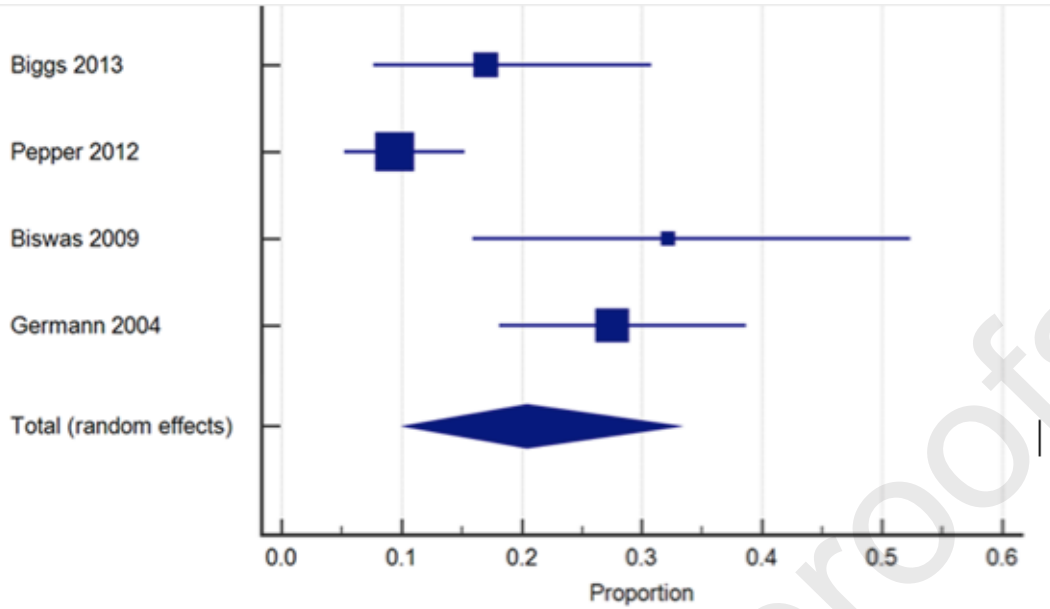
	With antibiotics	Without antibiotics
Total patients	223	160
Number of infection	1	1
Absolute risk	0.0045	0.00625
Absolute Risk Reduction (ARR)	0.00175	
95% Confidence Interval	(0.02 - 5.57)	
Number Needed to Treat (NNT)	571	



Study	Sample size	Proportion (%)	95% CI	Weight (%)
				Random
Murano 2019	69	0.000	0.000 to 5.206	18.52
Biggs 2013	47	0.000	0.000 to 7.549	12.70
Pepper 2012	149	1.342	0.163 to 4.765	39.68
Biswas 2009	28	0.000	0.000 to 12.344	7.67
Germann 2004	80	0.000	0.000 to 4.506	21.43
Total (random effects)	373	0.817	0.161 to 1.972	100.00

Test for heterogeneity

Q	1.5996
DF	4
Significance level	P = 0.8089
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 51.04



Study	Sample size	Proportion (%)	95% CI	Weight (%)
				Random
Biggs 2013	47	17.021	7.647 to 30.809	24.01
Pepper 2012	149	9.396	5.233 to 15.262	28.65
Biswas 2009	28	32.143	15.878 to 52.352	20.76
Germann 2004	80	27.500	18.104 to 38.624	26.59
Total (random effects)	304	20.418	10.309 to 32.897	100.00

Test for heterogeneity

Q	16.5521
DF	3
Significance level	P = 0.0009
I^2 (inconsistency)	81.88%
95% CI for I^2	53.06 to 93.00