Original Article

The role of BioGlue in thoracic surgery: a systematic review

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Background: BioGlue is a commonly used sealant in thoracic surgery. Prolonged air leak and presence of bronchopleural fistulae (BPF) are often encountered in clinical practice. We therefore, investigated the role and the efficacy of BioGlue in these scenarios.

Methods: A systematic review was conducted by searching Medline [1966–2016] and Cochrane Central Register of Controlled Trials (CENTRAL) [1999–2016] along with reference lists of the included studies. Included studies reported on thoracic surgery operations and use of BioGlue in thoracic surgical procedures, whereas excluded studies met at least one of the following criteria: non-English language studies, non-human population, studies on surgical specialties other than Thoracic surgery, reviews and meta-analyses and sealants other than BioGlue.

Results: Twelve studies with a total number of 194 patients were included. Amongst them, 178 were treated for alveolar air leaks (AAL), 14 for BPF and 2 for lymphatic leaks. BioGlue was utilized at the time of initial operation in 172 (96.7%) patients for AAL, while at secondary intervention in 13 (92.9%) for BPF and 1 (50%) for lymphatic leak. In terms of AAL, only 2 out of 4 studies showed statistically significant reduction in duration of air leak, duration of intercostal drainage and length of stay (LOS) when BioGlue was applied. No complications were encountered after using BioGlue in sealing BPF, apart from the re-application of BioGlue in 3 cases.

Conclusions: Although BioGlue has been shown to be efficient in treating AAL, it should be used with caution against BPF, despite encouraging preliminary results. Potential adverse effects must always be taken into consideration. Future randomized controlled trials are warranted in an attempt to establish its benefit in current clinical practice.

Keywords: BioGlue; thoracic surgery; air leak; bronchopleural fistulae (BPF)

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Introduction

Thoracic surgery has significantly evolved over the last 20 years achieving low mortality and morbidity rates. However, complications following thoracic operations still remain an issue and notably affect the postoperative course, with an added economical burden to health care systems (1). Amongst them, alveolar air leaks (AAL) and bronchopleural fistulae (BPF) are considered quite challenging in terms of management and lead to prolonged chest tube drainage,

LOS and increased risk of pleural infections (2,3).

Previous studies have shown that prolonged air leak, defined as seven days or more in duration, occur with high incidence after major thoracic operations (4). On the other hand, development of BPF, although presenting with a lower incidence, is associated with higher mortality rates (5). This has led to the development of several techniques to combat such complications. These include, but are not limited to, pleurodesis, placement of additional drains, thoracotomy and manual closure of the bronchial stump, intrathoracic muscle or omental flap transposition and use of different types of sealants, such as fibrin glue and Progel® (Neomend, Inc., Irvine, CA, USA) (6-8).

BioGlue® (CryoLife International Inc., Kennesaw, GA, USA) is an adhesive applied in several surgical specialties and its use has been documented in thoracic surgery as well. It consists of purified bovine serum albumin (BSA) and glutaraldehyde and produces a stable, solid medium after these two components bind to each other (9,10). In the present study, we systematically reviewed the literature regarding BioGlue in order to analyze its role in thoracic surgery and especially its application in the treatment of AAL and BPF.

Methods

Search strategy, data sources and eligibility criteria

The systematic review was conducted in accordance to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (*Table S1*) (11). The study protocol was discussed and agreed by all authors. A systematic literature search was performed using the Medline database and Cochrane library—Cochrane Central Register of Controlled Trials (CENTRAL) through July 2016; the terms "bioglue", "albumin-Glutaraldehyde tissue adhesive" and "sealants" were combined with the terms "thoracic", "lung", "air-leak" and "bronchial fistula".

Two authors (DI Tsilimigras, A Antonopoulou) worked independently and screened all available studies. The references of all relevant studies were manually assessed to avoid missing any available data.

The inclusion criteria consisted of: studies reporting on thoracic surgery operations and use of BioGlue in thoracic surgical procedures.

The exclusion criteria consisted of: non-English language studies, non-human population, studies on surgical specialties other than Thoracic surgery, reviews and meta-analyses and sealants other than BioGlue.

Data extraction and analysis

Two authors (DI Tsilimigras, A Antonopoulou) working separately extracted the data from the eligible studies and subsequently cross-checked the results. Any discrepancies were resolved following discussion and consensus amongst all participating authors. Variables that were extracted included: general study characteristics (author, year of publication, number of patients), patients demographics (sex, age, country), type of surgical procedure, indication for using BioGlue, concomitant use of BioGlue with other device/glue, duration of air leak, duration of chest tube drainage, LOS, complications and associated recurrence-free interval (RFI).

Results

The search algorithm yielded 252 studies and following screening, 73 studies were retrieved for full-text review. Twelve studies finally met our inclusion criteria and were included in the present systematic review (9,10,12-21). One study, although relevant, was eventually excluded due to reporting reasons (22) (*Figure 1*).

Features and demographics of the included studies are summarized in *Table 1*. Amongst them, seven articles were from UK, two from Greece, two from the USA and one from Australia. Overall, 194 patients were allocated with a 1:9 male to female ratio. Although BioGlue was used in a variety of Thoracic surgical procedures, the indications for application were mainly prolonged AAL and management of BPF. Four studies targeted the first indication (9,14-16), six studies the second (12,13,18-21), while in two studies both indications were analyzed (10,17) and these are presented separately. Regarding the prevention of air leak, BioGlue was mainly utilized at the time of initial operation (9,14-16), except for six cases (172/178), in whom prolonged air leak after primary procedure necessitated its application (10). On the other hand, BPF and lymphatic leak treatment was associated with secondary interventions in all but one case for each group [BPF: 13 (92.9%), lymphatic leak: 1 (50%)] following major thoracic surgery procedures (10,12,13,17-21).

Prevention of prolonged air leak

The four studies (9,14-16), referring exclusively to prevention of prolonged AAL, are summarized in *Table 2*.

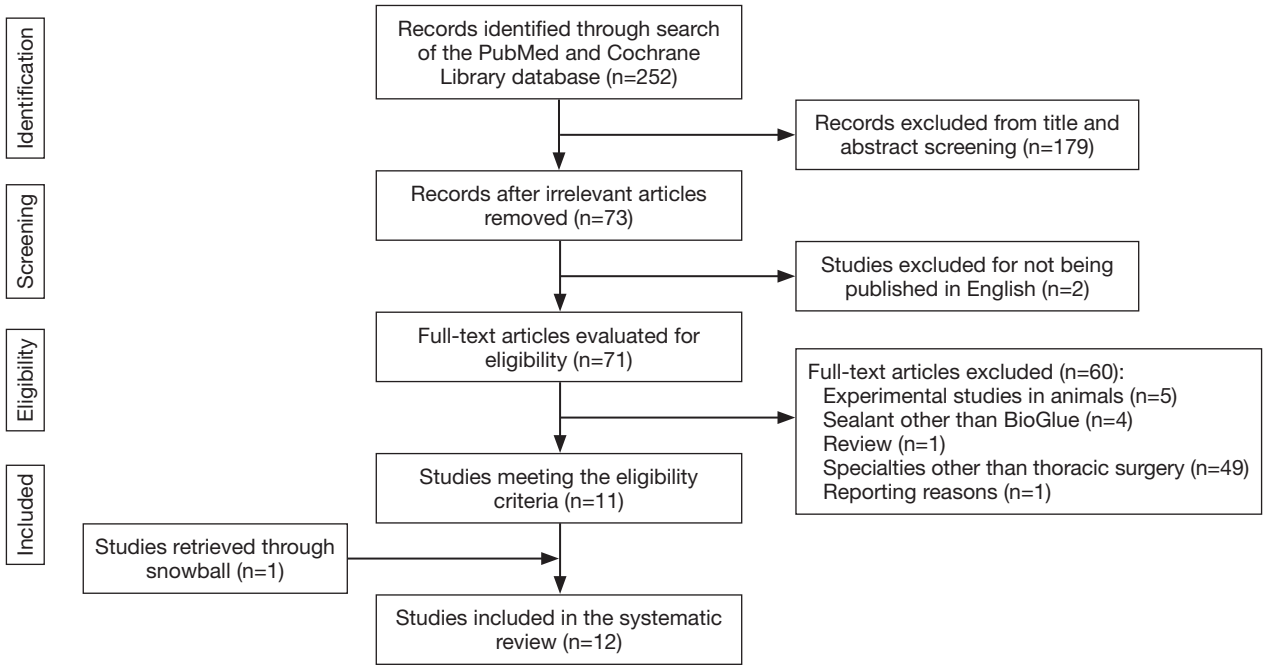

Figure 1 Flowchart of the search strategy.

In all cases, the application of BioGlue was performed at the time of initial operation. The indication for its use was failure to control the air leak by conventional means such as sutures, diathermy and stapling (9,14) as well as prevention of air leak after lung volume reduction surgery (LVRS) (15) and bullectomy (16).

In a prospective randomized controlled trial, Belcher *et al.* compared BioGlue and Vivostat for the control of AAL and showed no statistically significant difference regarding duration of air leak, duration of intercostal drainage, LOS and incidence of complications (14) (*Table 2*).

In another pilot randomized controlled trial, patients undergoing LVRS were randomized between receiving BioGlue or Peri-strips as an adjunct to the stapling line (15). Comparing the two arms of the study, the duration of air leak was 3±4.6 days (mean ± SD) in the BioGlue arm compared with 6.5±6.88 days in the Peri-strips arm (P=0.27), intercostal drainage was 733±404 versus 1,001±861 (P=0.65) and duration of intercostal drainage was 9.7±10.6 versus 11.5±11.1 days (P=0.73) in the two groups, respectively.

Tansley *et al.* compared two groups of patients; one was treated only surgically and the other was treated with BioGlue in addition to the standard surgical procedure (9). Patients from the latter group had shorter duration of air leak, intercostal drainage, and LOS, as shown in *Table 2*.

Finally, Potaris *et al.* applied BioGlue in 21 patients who underwent bullectomy and compared the results with an age- and sex-matched control group of similar patients (16). Duration of air leak was significantly shorter in the BioGlue group, as well as duration of intercostal drainage. The length of stay (LOS) was reduced but this did not reach statistically significant figure compared with the control group.

All complications in the BioGlue-treated groups of each study were not major and are outlined in *Table 2* as well.

Management of BPF

Six studies were included in this section (12,13,18-21) and their features are summarized in *Table 3*. In all cases, BPF treatment required secondary intervention. Amongst them, three studies refer to the treatment of BPF using an Amplatzer vascular occlusion device in combination with BioGlue application (12,13,21). Complications following this strategy were minor with two studies referring to re-application of BioGlue three days and three weeks after the initial procedure, respectively (13,21). Patients were all well after a follow-up period of 6 and 12 months in one (12) and 14 months in another study (13).

Lin *et al.* described the sealing of BPF with BioGlue in two patients who had undergone right pneumonectomy and

Table 1 Features and demographics of the studies included in the systematic review

Author [year]	Number of patients	Sex (M/F)	Age, years	Country	Surgical procedure	Indication for use
Bille [2012]	2	1/1	64 (M)/57 (F)	UK	1 left pneumonectomy, 1 right upper lobectomy	BPF (& left sided empyema)/BPF (& right sided empyema)
Spiliopoulos [2012]	1	1/0	63	UK	Left pneumonectomy	BPF
Belcher [2010]	50	28/22	57 [18–78] (mean, range)	UK	1 bilobectomy, 19 lobectomies, 2 lobectomies with lesser resection, 7 segmentectomies, 20 precision excision, 1 other	AAL
Rathinam [2009]	10	6/4	59.8 ±4.9 (mean ± SD)	UK	LVRS in end stage emphysema	AAL
Tansley [2006]	25	14/11	59 ±16 (mean ± SD)	UK	9 lobectomies, 3 lobectomies + lesser resection, 2 segmentectomies, 1 lingulectomy, 8 metastasectomies, 2 others	AAL
Potaris [2003a]	21	16/5	51.8 [23–76] (mean, range); median: 55	Greece	Bullectomy	AAL
Potaris [2003b]	38	29/9	51.4 [19–75] (mean, range); median: 57	Greece	36 thoracotomies, 1 rigid bronchoscopy, 2 VATS	AAL, BPF
Lin [2004]	2	0/2	21, 42	USA	1 pneumonectomy, 1 aortic root replacement for aortic coarctation (history of multiple thoracotomies)	Recurrent BPF (first was closed with staples and omental flap)
Passage [2005]	40	AAL: 27/ 9; BPF:2/0; lymph leak: 1/1	AAL: 1 month to 83 years; BFP: 56 (M), 54 (M); lymph leak: 19 (F), 73 (M)	Australia	AAL: 1 pneumonectomy, 10 lobectomies, 6 pleurodesis, 8 segment/wedge resections, 4 LVRS, 2 biopsies, 1 excision of mediastinal tumor, 2 pleural effusion drainages, 3 repairs of inadvertent lung injury during open heart surgery; BPF: 1 pneumonectomy, 1 pleuropneumonectomy; lymph leak: 1 haemangiolymphoma, 1 lobectomy	36 AAL, 2 BPF, 2 lymph leak
Lang-Lazdunski [2007]	1	0/1	53	UK	Right pneumonectomy	BPF [presented with empyema]
Ranu [2009]	3	1/2	70 (M), 55 (F), 63 (F)	UK	1 right middle and lower lobectomy,1 right lower lobectomy, 1 left pleuropneumonectomy	BPF
Gulkarov [2009]	1	1/0	68	USA	Right completion pneumonectomy	BPF

M, male; F, female; SD, standard deviation; UK, United Kingdom; USA, United States of America; LVRS, lung volume reduction surgery; VATS, video-assisted thoracic surgery; AAL, alveolar air leak; BPF, broncho-pleural fistulae.

Table 2 Prevention of prolonged air leak

Author [year]	Number of patients	Indication for use	Duration of air leak (days)	Duration of intercostal drainage (days)	LOS (days)	Complications	RFI (months)
Belcher [2010]	50	Failure of conventional attempts (sutures, stapling, diathermy) to control the air leak	Median (range): BioGlue, 3 (0–32) versus Vivostat, 2 (0–33) (P=0.677)	BioGlue: 5 [1–32] versus Vivostat: 5 [1–34] (P=0.473)	BioGlue: 8 [3–22] versus Vivostat: 7 [2–29] (P=0.382)	BioGlue: 20 patients versus Vivostat: 19 patients (P=0.839) Overall 20/50 patients (40%) had complications; prolonged air leak (9/50=18%), pleural space infection (4/50=8%), others (7/50=14%)	NR
Rathinam [2009]	10	Pilot clinical trial aiming at reducing AAL	Mean ± SD: BioGlue, 3.0±4.6 versus peri-strips, 6.5±6.88 (P=0.27)	BioGlue: 9.7±10.6 versus peri-strips: 11.5±11.1 (P=0.73)	NR	None	NR
Tansley [2006]	25	Failure of conventional measures to control the air leak	Median (range): BioGlue, 1 (0–2) versus surgical-alone group, 4 [2–6] (P<0.001)	BioGlue: 4 [3–4] versus surgical-alone group: 5 [4–6] (P=0.012)	BioGlue: 6 [5–7] versus surgical-alone group: 7 [7–10] (P=0.004)	BioGlue: 2 prolonged AAL, 1 diarrhea, 2 clinically unimportant pneumothoraces after the initial intercostal chest drain removal, 1 pneumothorax requiring further intercostal drain insertion, 2 prolonged fluid drainage	NR
Potaris [2003a]	21	Prevention of air leak after bullectomy	Median (range): BioGlue, 0.42 (0–2) versus control group, 3.68 [2–11] (P<0.001)	BioGlue: 2.33 [2–4] versus control group: 5.42 [3–12] (P<0.05)	BioGlue: 5.1 [4–7] versus control group: 9.52 [7–27] (P>0.05)	BioGlue: none (respiratory failure, atrial fibrillation maybe not attributable to BioGlue)	Mean: 12+ (follow up range, 1–23)

M, male; F, female; SD, standard deviation; AAL, alveolar air leak; UK, United Kingdom; LVRS, lung volume reduction surgery; LOS, length of stay; RFI, recurrence-free interval; NR, not reported.

Table 3 Management of bronchopleural fistulae

Author [year]	Number of patients	Surgical procedure	Other device/glue used with BioGlue	Site of application-application procedure (technique)	LOS (days)	Complications	RFI (months)
Bille [2012]	2	1 left pneumonectomy, 1 right upper lobectomy	22 F Amplatzer vascular occlusion device	Left main bronchus/right upper lobe bronchus—both under combined bronchoscopic and thoracoscopic vision	1	None	12+, 6+
Spiliopoulos [2012]	1	Left pneumonectomy	Amplatzer II vascular plug, autologous blood clot injection to block the proximal part of the plug	Left main bronchus-fluoroscopically-guided, transbronchial embolization of the fistula	5 (3 after initial operation + 2 after additional use of BioGlue)	3 days after the procedure, a small amount of air leak was noted, 10 mL of BioGlue were additionally applied through VATS	14+
Gulkarov [2009]	1	Right completion pneumonectomy	A 10-mm Amplatzer septal occluder device	In the middle of the right bronchial stump—through the Eloesser flap	30 (1 month)	1 re-application after 3 weeks	NR
Lin [2004]	2	1 right pneumonectomy, 1 aortic root replacement for aortic coarctation (history of multiple thoracotomies)	No	Right main bronchial stump-rigid bronchoscopy/ NR-ureteroscope through chest tube	NR, 6	None	5+, 1+
Lang-Lazdunski [2007]	1	Right pneumonectomy	No	Right main bronchial stump-thoracotomy reopened	NR	None	24+
Ranu [2009]	3	1 right middle and lower lobectomy, 1 right lower lobectomy, 1 left pleuropneumonectomy	No	Right main bronchial stump/right lower lobe bronchial stump/left main bronchial stump—all through rigid bronchoscope	NR, 1, 5	On day 11, a smaller defect was identified and was re-sealed with BioGlue, subsequent Aspergillus fumigatus infection within the pleural space; none; none	NR, 3+, 3+

M, male; F, female; UK, United Kingdom; USA, United States of America; LOS, length of stay; RFI, recurrence-free interval; NR, not reported.

aortic root replacement respectively. No complications were encountered postoperatively as well as after one and five months respectively (18).

In addition, Lang-Lazdunski described the successful closure of a small BPF after injection of BioGlue on the right main bronchial stump following pneumonectomy. No recurrence was recorded at two years follow-up (19).

Ranu *et al.* reported the application of BioGlue in three patients who had developed BPF after major thoracic operations (20). One of them developed a smaller defect on day 11, which was eventually sealed by re-application of BioGlue. At follow-up, two patients remained well, while the third, despite subsequent pleural infection, had the bronchial stump intact at repeat bronchoscopy.

Mixed studies

Two studies were found to present combined results; hence they are described in a distinct category (10,17).

In the study by Potaris *et al.*, BioGlue was applied in 38 patients, with mean air leak duration of 0.6 days (range, 0–2 days); mean intercostal drainage of 3.4 days (range, 1–12 days) and median hospitalization of 6 days (range, 4–16 days). Amongst them, BPFs in two patients were sealed after primary operation using BioGlue, with air leak lasting 0 and 2 days. Overall, complications occurred in three patients with atelectasis in one and residual space in two (17).

Passage *et al.* applied BioGlue for AAL in 36 patients, BPF in 2 and lymph leak in 2 patients (10). In the AAL-group, BioGlue was used in 30 patients during the primary procedure, while persistent air leak necessitated its application after primary operation in six cases. Time from initial procedure to re-intervention was 7.7 days (range, 1–21 days), hospital stay was 10 days (range, 1–78 days) and mean duration of intercostal drainage was 4 days. BioGlue controlled the air leak in all but one patient, who eventually died from respiratory failure on the 19th postoperative day. In addition, two patients required re-application of glue, one developed empyema and two developed pneumonia postoperatively. Finally, in the BPF and lymph leak groups, the application of BioGlue was performed during the primary procedure in one patient of each group and it was proved effective in the half of each group's cases (10).

Discussion

BioGlue is a commonly used surgical sealant in thoracic surgery. Our review points out that the main indications for its application are prevention of AAL and management of BPFs. As revealed by the included studies, no superior efficacy of BioGlue was shown, compared with other adjuncts such as Vivostat (14) and Peri-strips (15). We observed though a significant reduction in the duration of air leak, intercostal drainage and LOS when compared with surgical intervention alone (9,16).

In managing BPFs, BioGlue was applied in only fourteen patients (10,12,13,17-21), of which three received an Amplatzer device as well (12,13,21). No major complications were recorded. However, due to the small sample of patients, no definite conclusions concerning its efficacy can be drawn.

Prolonged air leak is considered the most common complication following thoracic surgery operations (23). Drahush *et al.* proposed a standardized approach to reduce prolonged air leak after pulmonary resection, consisting of "fissure-last" surgical technique, staple line buttressing and protocol-driven chest tube management postoperatively. Their results revealed a 52% reduction in the incidence of air leak in comparison with the Society of Thoracic Surgeons National Database figures (24).

At a recent meta-analysis, the intraoperative use of surgical sealants or adjuncts reduced the incidence of prolonged air leak postoperatively (25). However, BioGlue was not included in the list of utilized adjuncts. In our review, only two studies showed statistically significant results in terms of duration of air leak, intercostal drainage and LOS, following the use of BioGlue (9,16).

Another issue that merits special consideration is the management of BPF, which usually present with a lower incidence after thoracic operations but yet have a detrimental effect on patient outcomes.

In terms of management, we reported three studies, in which BPFs were treated with an Amplatzer vascular occlusion device in combination with BioGlue (12,13,21). A recent case report described the treatment of a large BPF with the same device (Amplatzer) without applying BioGlue but with similar results (26). Fuso *et al.* compared two groups of patients who developed BPFs, one treated conservatively and a second undergoing conservative treatment plus endoscopic application of different glues (27). The results revealed a shorter resolution time in the combined-treated group (15.4±13.2 *vs.* 25.8±13.2 days, P=0.299), which though not statistically significant, was related to a larger fistula size. In general, large BPFs (>8 mm) are not considered suitable for endoscopic management, whereas smaller BPFs are more likely to heal properly (28). Unfortunately, our studies did not provide details on the size of BPF and therefore no

firm conclusions can be drawn on the efficacy of BioGlue in sealing any size of BPF.

Since video-assisted thoracoscopic surgery (VATS) is becoming the dominant modality in thoracic surgery, application of BioGlue may be possible through less invasive approaches. In our review, one study referred to successful application of BioGlue in two cases during VATS, one after wedge resection and the other following an iatrogenic lung laceration (17). However, most of the studies reporting on the prevention of AAL did not provide details on the surgical procedures that were implemented. Furthermore, the vast majority of studies concerning the treatment of BPF reported the application of this adjunct through an endoscopic approach (12,13,18,20). The variability in applicator lengths renders the use of this glue feasible not only during thoracotomies but also during VATS or rigid bronchoscopy (17). Despite the limited evidence to date, no technical restrictions seem to emerge with regards to the application procedure, thus suggesting the applicability of BioGlue during minimally invasive approaches.

There remain concerns about the safety of BioGlue due to its non-human nature. In general, BioGlue comprises of two components, purified BSA and glutaraldehyde which produce a mechanical seal when bound to each other (29). This seal remains rigid and does not expand with the underlying lung parenchyma resulting in increased risk of translocation and re-establishment of air leak. Additionally it has a low bio absorbability (14,17,19), while its non-autologous nature can trigger an inflammatory response (30), with risk of toxicity (31) and lung fibrosis (32).

Conclusions

BioGlue seems to be used by the Thoracic Community for the prevention of AAL and less frequently for the management of BPF. Although small randomized controlled trials quote its efficiency in the management of AAL, its benefit in treating BPF has yet to be proven through studies with a larger cohort of patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 PRISMA 2009 checklist

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	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	3
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	3, 4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	4
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	Not applicable
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	Not applicable
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis	Not applicable