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REVIEW ARTICLE

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The efficacy and safety of therapeutic lung lavage for exogenous lipoid pneumonia: A systematic review

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Abstract

Introduction and objectives: Exogenous lipoid pneumonia (ELP) is a lung inflammatory disease with low prevalence and has the feature of external lipid substances presented in the alveoli. Therapeutic lung lavage (segmental bronchoalveolar lavage and whole lung lavage) has been gradually recognized as an important therapy for the disease. There was no comprehensive summary on its efficacy and safety.

Methods: We searched PubMed, Embase, Cochrane Library, CNKI, Wanfang Database, clinicaltrials.gov, and the references of included studies. After study selection, data extraction and quality assessment, we performed a qualitative description of current data.

Results: We included 90 ELP patients from 25 case reports and 8 case series studies. Eighty-four (93.3%) patients received segmental bronchoalveolar lavage and six (6.7%) patients received whole lung lavage. Eighty-seven (96.7%) patients got clinical improvement after lavages, while three (3.3%) patients had no improvement and eventually died. The follow-up status was reported in 29 patients, of whom 24 patients remained well without any use of drugs and 4 patients remained well with some periods of corticosteroids. One patient endured recurrence. The radiological change was reported in 72 patients, of whom 41 (56.9%) patients had full resolution until the last follow-up. Two studies reported acute pulmonary edema and transient hypoxemia during lavages.

Abbreviations: BALF, bronchoalveolar lavage fluid; CRP, C-reactive protein; CT, computer tomography; ELP, exogenous lipoid pneumonia; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; sBAL, segmental bronchoalveolar lavage; WBC, white blood cell count; WLL, whole lung lavage.

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Conclusions: Therapeutic lung lavage might be an effective and safe therapy with long-term benefits for ELP. Current studies were all case reports and case series with relatively high risk of bias. Prospective controlled studies are needed to explore the actual efficacy, safety, individualized indications, and optimized treatment procedures of therapeutic lung lavage for ELP.

KEYWORDS

bronchoalveolar lavage, exogenous lipoid pneumonia, systematic review, therapeutic lung lavage, whole lung lavage

1 | INTRODUCTION

Exogenous lipoid pneumonia (ELP) refers to a pulmonary inflammatory disease with low prevalence, and is ascribed to the aspiration or inhalation of external lipid substances.[1] Microscopically, intracellular lipid (eg, lipid-laden macrophages), or extracellular floating lipid substances can be observed in the alveoli.[1] Common symptoms of ELP include cough, fever, and dyspnea, while some patients remain asymptomatic.[2] Pulmonary radiological findings of ELP are not specific, and vary in patterns and distributions among different patients.[3] Common computed tomography (CT) manifestations include ground-glass opacity, consolidation, and interlobular septal thickening, and the distribution might be segmental or lobar, unilateral or bilateral.[2,3]

The treatment of the disease is not standardized, and no evidence-based guideline for ELP has been published. Common interventions include discontinuation of lipid exposure, corticosteroids, antibiotics, and therapeutic lung lavage.[4,5] Therapeutic lung lavage has been gradually recognized as an important therapy for ELP. Based on the conditions and complications of the patients, segmental bronchoalveolar lavage (sBAL) or whole lung lavage (WLL) is often performed. In sBAL, the lavage fluid such as normal saline is instilled into the lungs and subsequently suctioned out from the same route using the bronchoscope, while for WLL, the lavage fluid is removed from the lungs by gravitational drainage, during which course the target substances, such as aspirated materials and inflammatory factors can be cleared by the lavage fluid.[6,7] Both sBAL and WLL were reported to be effective in some case reports and case series.[1,3] Compared with WLL, sBAL is safer and can be performed with a more simple procedure, while WLL has the potential to be more powerful in clearing the inhaled/aspirated substances and inflammatory factors.[8,9]

Despite the isolated reports on the efficacy of lung lavage, no systematic summary of efficacy was provided by previous studies. Besides, there were limited data on the patient characteristics, clinical presentation, diagnosis, and treatment details in patients with ELP treated by therapeutic lung lavage. We conducted a systematic review to summarize the existing literature on therapeutic lung lavage for treating ELP patients and evaluate the efficacy and safety of therapeutic lung lavage for ELP.

2 | MATERIALS AND METHODS

We performed a systematic review under the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline.[10] The review protocol was registered in PROSPERO (International prospective register of systematic reviews). The registration number is CRD42019137823.

2.1 | Literature search and study selection

We searched the PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Database from inception date to June 24, 2019. Terms related to population (exogenous lipoid pneumonia) and intervention (sBAL or WLL) were used to establish the search strategy. We also screened the references of included studies and clinicaltrials.gov for additional records. The detailed search strategy was described in Table S1.

The target population was patients diagnosed with ELP. The target intervention was therapeutic lung lavage, including both therapeutic sBAL and WLL. Patients only receiving diagnostic bronchoalveolar lavage were not included. The target outcome included clinical improvement, mortality (for case reports and case series studies, the number of death events), follow-up status, radiological improvement, lung function, patient safety, and quality of life. The exclusion criteria were: (1) Studies in which the clinical outcome of patients receiving lung lavage was unknown. (2) Conference abstracts.

Two investigators (L.S. and S.D.) independently screened the titles and abstracts of potentially eligible studies. After the screening process, they assessed the full-texts of those potentially eligible studies. The disagreements between them over study selection, as well as next steps (data extraction and

quality assessment), were resolved through discussion or consultation from a third investigator (X.G.), where necessary.

2.2 | Quality assessment

As the eligible studies were all case reports or case series studies, the methodological quality was assessed by the applicable items from "Tool for evaluating the methodological quality of case reports and case series", a quality assessment tool proposed by Murad and his colleagues.[11] Two investigators (L.S. and S.D.) assessed the quality of included studies from selection, ascertainment, causality, and reporting.[12-14] The four domains contained five items with binary responses applicable for this systematic review. Studies with five, four, three, or less items fulfilled were considered to be with high, moderate, and low quality, respectively.

2.3 | Data extraction and analysis

Two investigators (L.S. and S.D.) extracted the data from included articles with a standardized data collection form. To minimize the heterogeneity in data extraction, we developed a detailed data collection form with specific definition of possibly confusing items (Table S2). The key components of the data extraction form included basic study information, quality assessment, patient characteristics, intervention details, and outcomes. For the clinical improvement outcome, we defined a patient clinically improved if the patient met either of the two criteria after the lavage: (1) The authors reported clinical improvement in the paper. (2) The authors reported symptoms alleviation with decrease in inflammatory factors or improvement in radiological findings. Besides, we documented two kinds of interval in lavage. Onset-lavage interval referred to the interval between lavage and onset of symptoms or the presentation of radiological changes in patients without symptoms. Admission-lavage interval referred to the interval between lavage and the admission to the hospital. Specific definitions of other terms (eg, outcomes, intervention details, etc.) can be found in Table S2. During data extraction process, there were two types of unavailable data: (1) The data item was not presented in the literature. (2) The data items were only provided at aggregated level but not individual level, so information (such as age and sex) only for the patients receiving lung lavage was not available if not all patients received lung lavage treatment. The unavailable data were recorded as "unknown."

The eligible studies were all case reports and case series studies, and quantitative synthesis of data (meta-analysis) were not feasible. Therefore, we conducted a qualitative description which summarized the patient characteristics, diagnosis, intervention details, and reported outcomes. The data from included case reports and case series were summarized and reported as frequency and percentage.

3 | RESULTS

3.1 | Study selection and characteristics of included studies

The literature search on June 24, 2019 identified 883 records, of which 740 were retained after duplication removal. After screening of titles and abstracts, 189 records remained for full-text assessment. Finally, 36 reports were eligible.[15-50] Based on the information from the method part (eg, the data collection date and the research site), three reports from Sias et al.[20,22,23] and two reports from Zhou and Deng et al.[21,24] were considered to be from the same case series studies, respectively. Therefore, 33 studies (25 case reports and 8 case series) were eligible for data extraction.[15-19,21,22,25-50] During the data extraction prcess, the missing information of the main reports were complemented by the other reports from the same case series.[20-24] The detailed flow of study selection was depicted in Figure 1. The characteristics of included studies were described in Table 1. Only the patients receiving lung lavage therapy were counted in the number of cases.

3.2 | Quality assessment of included studies

The detailed information of quality assessment was described in Table 2. There were 19 and 14 of the eligible studies with moderate and low quality, respectively. The studies performed relatively well in the causality and ascertainment domains. The follow-up duration in most studies was considered enough for the outcomes to happen. However, most of the studies (31/33, 93.9%) did not report the selection process, and many studies (15/33, 45.5%) failed to provide adequate details of lung lavage, which resulted in the relatively low methodological quality.

3.3 | Patient characteristics

The characteristics of the 90 patients from the 33 studies were described in Table 3. Sixty-four (71.1%) included patients were children, while 26 (28.9%) were adults. The most prevalent aspirated substance in these patients was the mineral oil (79 patients [92.9%]). In many cases, the aspiration of mineral oil was related to the mineral oil therapy treating bowel obstruction. Another important source was the gas siphoning in some countries such as China and India. Among patients (n = 52) with information related to underlying diseases, 30 (57.7%) were reported to have underlying diseases

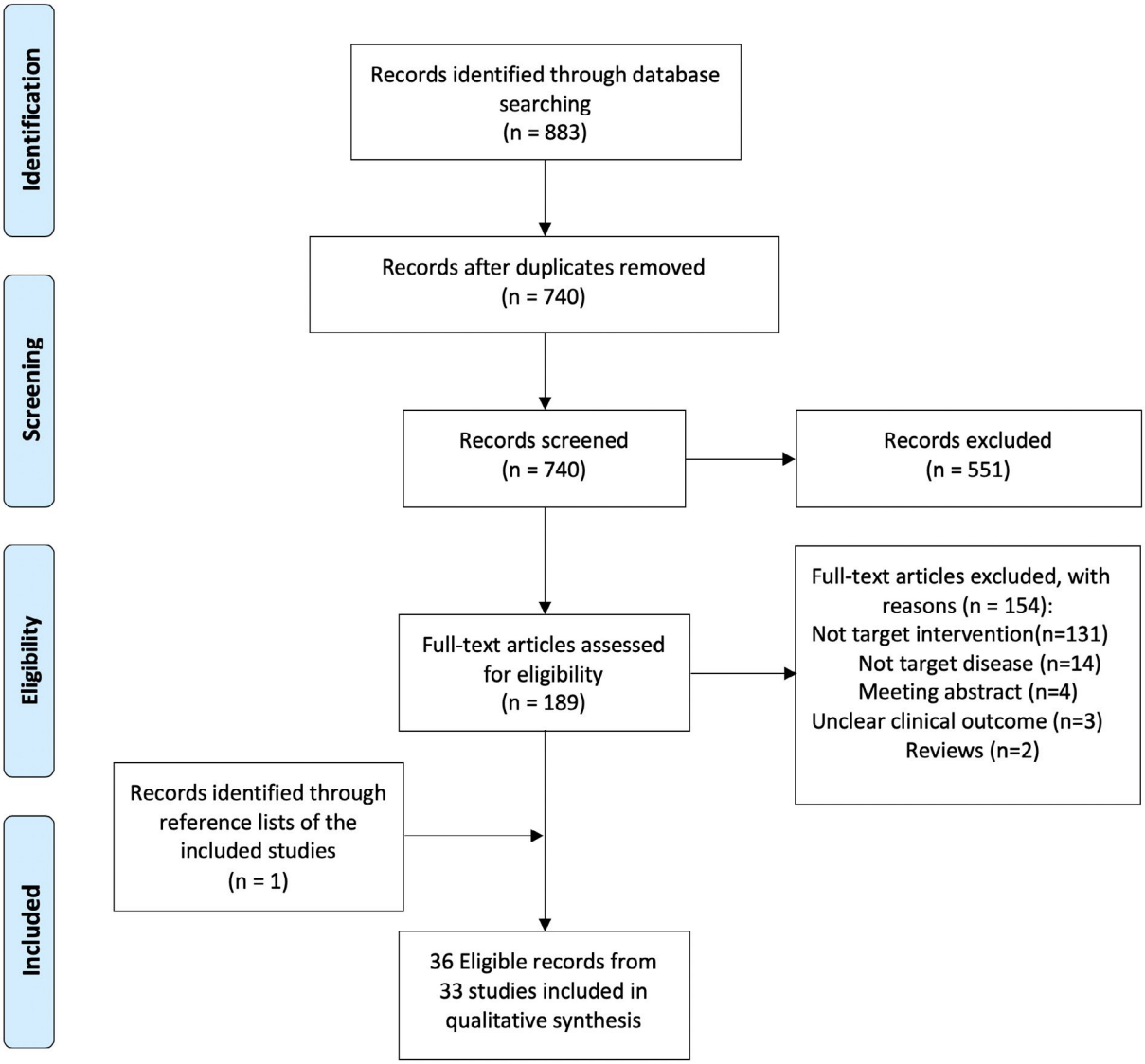

FIGURE 1 The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow chart

such as bowel obstruction, parasite infection, and deglutition disorders, and the remaining 22 (42.3%) were reported to have no underlying diseases.

The most frequently reported symptoms were cough/sputum, fever, and dyspnea. The inflammatory indicators such as white blood cell count (WBC), C-reactive protein (CRP), procalcitonin (PCT), and erythrocyte sedimentation rate (ESR) were reported in some patients, most of whom experienced an elevation in the indicators. The detailed normal range of the inflammatory indicators were listed in the table legend of Table 3[51-53]. The microbiological findings were reported in 41 patients, of whom only 7 (17.1%) patients were reported positive in respiratory specimens and the 3 patients receiving WLL all had negative results. As for diagnosis, history of aspiration was referred to in 89 (98.9%) patients. The patient in Wong 1994 had the psychiatric disease and did not provide the history of intentional aspiration of mineral oil.[46] All patients received radiological tests, either CT or chest X-ray. The diagnosis by bronchoalveolar lavage fluids (BALF) cytology referred to the presence of lipid-laden macrophages and/or extracellular lipid substances in BALF confirmed by oil red O stain or Sudan stain.[54,55] The diagnosis by BALF cytology was reported in 40 patients (44.4%).

3.4 | Details of intervention

Table 4 described the interventions in detail. Eighty-four (93.3%) patients received sBAL and six (6.7%) patients received WLL. The most frequently used lavage fluid was normal saline (88 patients [97.8%]). Two patients received other types of fluid: "Emulsifier" (0.05% polysorbate 80 in Ringer's lactate) and "8% $NaHCO_3$+0.02% Nitrofurazone".[43,49] Lavage volume was reported in 72 patients, of whom 33 (45.8%) patients with recorded volume received weight-dependent volume of lavage fluid, ranging from 0.5 mL/kg to 2 mL/kg.[16,22,25]

TABLE 1 The characteristics of included studies

Study ID	Study type	N	Age	Lavage	Clinical improvement	In-hospital death	Follow-up		
							Recurrence	Time	Drug
Marangu 2018[15]	Case series	5	Children	sBAL	5	0	NR	NR	NR
Zeng 2015[16]	Case series	6	Children	sBAL	6	0	0	NR	No
Zhao 2015[17]	Case series	4	Children	sBAL	4	0	NR	NR	Corticosteroids*
Chen 2014[18]	Case series	4	Adults	sBAL	4	0	NR	NR	NR
Qiu 2013[19]	Case series	2	Adults	sBAL	2	0	NR	NR	NR
Deng 2010[21]	Case series	19	Children	sBAL	19	0	0†	1yr	No
Sias 2009[22]	Case series	20	Children	sBAL	20	0	NR	NR	NR
Li 2007[25]	Case series	3	Children	sBAL	2	1	NR	NR	NR
Zhong 2019[26]	Case report	1	Adults	sBAL	1	0	NR	NR	NR
Wang 2018[27]	Case report	1	Adults	sBAL	1	0	NR	NR	NR
Wu 2018[28]	Case report	1	Adults	WLL	0	1	–	–	–
Kim 2018[29]	Case report	1	Adults	sBAL	1	0	1	7w	Corticosteroids (6w)
Wong 2018[30]	Case report	2	Adults	sBAL	2	0	0	1yr	No
Tukaram 2018[31]	Case report	1	Children	sBAL	1	0	0	6w	No
Ye 2016[32]	Case report	1	Adults	sBAL	1	0	NR	NR	NR
Lau 2016[33]	Case report	1	Adults	WLL	1	0	0	NR	No
Chen 2015[34]	Case report	1	Adults	sBAL	1	0	NR	NR	NR
Sachdev 2015[35]	Case report	1	Children	sBAL	1	0	0	6mo	Corticosteroids
Kuroyama 2015[36]	Case report	1	Adults	sBAL	1	0	0	8mo	Corticosteroids
Nakashima 2015[37]	Case report	1	Adults	sBAL	1	0	0	2yr	No
Modaresi 2015[38]	Case report	1	Children	sBAL	1	0	NR	NR	NR
Guarachi 2014[39]	Case report	1	Adults	sBAL	1	0	0	1yr‡	Corticosteroids
Zeng 2014[40]	Case report	1	Adults	sBAL	1	0	NR	NR	NR
Wang 2013[41]	Case report	1	Adults	sBAL	1	0	0	1mo	No
Simoes 2012[42]	Case report	1	Children	sBAL	1	0	0	NR	No
Russo 2006[43]	Case report	1	Adults	WLL	1	0	NR	NR	NR
Zhang 2001[44]	Case report	1	Children	sBAL	1	0	NR	NR	NR
Ciravegna 1997[45]	Case report	1	Children	WLL	1	0	0	40d	No
Wong 1994[46]	Case report	1	Adults	WLL	1	0	With psychological disease, the patient intentionally aspirated liquid paraffin and eventually died§.		
Chang 1993[47]	Case report	1	Adults	WLL	1	0	0	6mo	Corticosteroids (3mo)
Wang 1991[48]	Case report	2	Adults	sBAL	2	0	NR	NR	NR
Xia 1989[49]	Case report	1	Adults	sBAL	1	0	NR	NR	NR
Oliveira 1985[50]	Case report	1	Children	sBAL	0	1	–	–	–

Abbreviations: d, day; mo, month; NR, Not reported; w, week; yr, year.

*In this paper, the authors only described that they prescribed corticosteroids for patients after discharge. The length and status of follow-up was not described. Thus, the four patients were not included in the follow-up recurrence analysis.

†Among 19 patients in the study, 10 patients were followed.

‡The patient underwent 10 times of lavage in the first 10 weeks.

§Because the patient intentionally aspirated lipid substances due to psychological disorder, she was not included in the follow-up recurrence analysis.

TABLE 2 The methodological quality of included studies

Study ID	Study type	Selection*	Ascertainment		Causality	Reporting	Overall†
			Exposure	Outcome			
Marangu 2018[15]	Case series	+	+	+	+	−	?
Zeng 2015[16]	Case series	−	+	+	+	+	?
Zhao 2015[17]	Case series	−	+	−	−	−	−
Chen 2014[18]	Case series	−	−	+	+	−	−
Qiu 2013[19]	Case series	−	−	−	+	−	−
Deng 2010[21]	Case series	−	+	+	+	−	−
Sias 2009[22]	Case series	+	+	+	+	−	?
Li 2007[25]	Case series	−	+	−	+	−	−
Zhong 2019[26]	Case report	−	−	+	+	−	−
Wang 2018[27]	Case report	−	−	+	+	−	−
Wu 2018[28]	Case report	−	−	+	+	−	−
Kim 2018[29]	Case report	−	+	+	+	+	?
Wong 2018[30]	Case report	−	+	+	+	+	?
Tukaram 2018[31]	Case report	−	+	+	+	+	?
Ye 2016[32]	Case report	−	+	+	+	+	?
Lau 2016[33]	Case report	−	+	+	+	+	?
Chen 2015[34]	Case report	−	−	+	−	−	−
Sachdev 2015[35]	Case report	−	+	+	+	+	?
Kuroyama 2015[36]	Case report	−	+	+	+	+	?
Nakashima 2015[37]	Case report	−	+	+	+	+	?
Modaresi 2015[38]	Case report	−	+	+	+	+	?
Guarachi 2014[39]	Case report	−	+	+	+	+	?
Zeng 2014[40]	Case report	−	+	+	+	+	?
Wang 2013[41]	Case report	−	+	+	+	+	?
Simoes 2012[42]	Case report	−	+	+	+	−	−
Russo 2006[43]	Case report	−	+	+	+	+	?
Zhang 2001[44]	Case report	−	+	+	−	−	−
Ciravegna 1997[45]	Case report	−	+	+	+	+	?
Wong 1994[46]	Case report	−	+	+	+	+	?

(Continues)

TABLE 2 (Continued)

Study ID	Study type	Selection*	Ascertainment		Causality	Reporting	Overall†
			Exposure	Outcome			
Chang 1993[47]	Case report	🔴	🟢	🟢	🟢	🟢	🟡
Wang 1991[48]	Case report	🔴	🔴	🔴	🟢	🔴	🔴
Xia 1989[49]	Case report	🔴	🟢	🔴	🟢	🟢	🔴
Oliveira 1985[50]	Case report	🔴	🟢	🟢	🟢	🔴	🔴

Criteria[11]**: Selection:** question 1: Did the patient(s) represent the whole experience of the investigator or is the selection method unclear to the extent that other patients with similar presentations may not have been presented?; **Ascertainment:** question 2: Was the case adequately ascertained?, question 3: Was the outcome adequately ascertained?; **Causality:** question 4: Was follow-up long enough for outcomes to occur?; **Reporting**: question 5: Is the case described with sufficient details to allow practitioners to make inferences on their own practice?

*For the answer of each question: 🟢:Yes; 🔴: No.

†For the overall methodological quality: 🟢: High quality; 🔴: Moderate quality; 🟡: Low quality.

As for WLL, except an 8-year-old boy receiving 600 mL lavage fluid,[45] patients receiving WLL all had large volume of lavage fluids, ranging from 8.7 L to 21 L.[28,33,43,46,47] The onset-lavage interval was reported in 24 patients, among whom 19 (79.2%) patients received lavage within 1 month of symptom onset. The admission-lavage interval was reported in 12 patients. Six (50%) patients received lavage within 1 week of admission, while nine patients (75%) received lavage within 1 month. The times of lavage were reported in 39 patients, of whom 30 (76.9%) patients received one lung lavage. Most patients (83.3%) receiving WLL were treated with only one time of lung lavage. Important co-therapies such as antibiotics and corticosteroids were reported in 63 patients.

3.5 | Outcomes

The clinical status of all included patients was reported. Eighty-seven (96.7%) patients got clinical improvement. Three (3.3%) patients died. The follow-up status was reported in 29 patients and the follow-up period ranged from 40 days to 2 years. Among them, 24 patients remained well without any use of drugs and 4 patients remained well with some periods of corticosteroids. One patient endured recurrence, then was treated with corticosteroids for 6 weeks.[29] For radiological changes, the results of the last follow-up in the included studies were extracted. The radiological change was reported in 72 patients, of whom 41 (56.9%) patients had full resolution and 31 (43.1%) patients had partial resolution until the last follow-up. The lung function was reported in 10 patients and all the patients were fully recovered. Two studies reported adverse events. Wu et al. reported acute pulmonary edema during the WLL process.[28] Sias et al. reported transient hypoxemia during the sBAL procedure which recovered after the sBAL.[23] The quality of life was not reported in any patient.

4 | DISCUSSION

To our knowledge, this is the first systematic review summarizing the efficacy and safety of therapeutic lung lavage for ELP. We included 90 patients from 25 case reports and 8 case series. The results suggest that lung lavage might be a potentially effective and safe therapy with long-term benefits for ELP, as most (96.7%) of the reported patients clinically improved with few adverse events reported and low recurrence rate. However, as the included studies were of low to moderate quality, did not have control in design and might have publication bias, the results should be interpreted with caution and prospective, controlled studies are necessary in the future.

Therapeutic lung lavage has been used in various respiratory diseases. Meconium aspiration syndrome (MAS) refers to a disease featured by the inhalation or aspiration of amniotic fluid mixed with meconium into fetuses' lungs in the uterus or newborns' lungs at delivery.[56] Animal models suggest that sBAL has the ability to remove the meconium inhaled into the lungs, thus increasing oxygen saturation and improving lung function.[56,57] A Cochrane systematic review of randomized controlled trials reveals the therapeutic role of segmental lung lavages with exogenous surfactant.[7,58] Pulmonary alveolar proteinosis is featured by the accumulation of surfactants in pulmonary alveoli which prevent normal gas-exchange.[59,60] WLL has been a successful treatment recommended for pulmonary alveolar proteinosis.[61] Besides, in patients with high risk of WLL-related complications, sBAL has also been reported to be effective.[62] In patients with aspiration pneumonia receiving mechanical ventilation, early sBAL has been reported to be associated with lower mortality.[63] The main mechanism behind the therapeutic effects of lung lavage in these diseases might be its ability to clear aspirated substances, inflammatory factors caused by immune responses, and surfactants, which might impair the

TABLE 3 The general characteristics of included patients

Feature	n/N (%)*		
	Overall	**sBAL**	**WLL**
Age			
Adult	26/90 (28.9)	21/84 (25)	5/6 (83.3)
Children	64/90 (71.1)	63/84 (75)	1/6 (16.7)
Sex			
Male	35/65 (53.8)	34/59 (57.6)	1/6 (16.7)
Female	30/65 (46.2)	25/59 (42.4)	5/6 (83.3)
Aspirated substances			
Mineral oil	79/85 (92.9)	74/79 (93.7)	5/6 (83.3)
Plant oil	5/85 (5.9)	4/79 (5.1)	1/6 (16.7)
Animal oil	1/85 (1.2)	1/79 (1.3)	0/6 (0)
Underlying diseases			
Bowel obstruction	18/52 (34.6)	17/46 (37.0)	1/6 (16.7)
Parasite infection†	5/52 (9.6)	5/46 (10.9)	0/6 (0)
Constipation‡	1/52 (1.9)	0/46 (0)	1/6 (16.7)
Deglutition disorders	7/52 (13.5)	6/46 (13.0)	1/6 (16.7)
Cancer	4/52 (7.7)	4/46 (8.7)	0/6 (0)
Psychiatric disorders	2/52 (3.8)	0/46 (0)	2/6 (33.3)
Suspected immune deficiency	1/52 (1.9)	0/46 (0)	1/6 (16.7)
No disease	22/52 (42.3)	21/46 (45.7)	1/6 (16.7)
Clinical findings			
Cough/Sputum	58/67 (86.6)	53/61 (86.9)	5/6 (83.3)
Fever	57/68 (83.8)	53/63 (84.1)	4/5 (80)
Dyspnea	55/69 (79.7)	49/63 (77.8)	6/6 (100)
Respiratory Failure	21/39 (53.8)	17/35 (48.6)	4/4 (100)
WBC elevation§	35/39 (89.7)	34/38 (89.5)	1/1 (100)
CRP elevation§	13/14 (92.9)	13/14 (92.9)	0/0
PCT elevation§	7/9 (77.8)	6/8 (75)	1/1 (100)
ESR elevation§	6/7 (85.7)	6/7 (85.7)	0/0
Positive microbiological findings	7/41 (17.1)	7/38 (18.4)	0/3 (0)
Diagnosis			
History	89/90 (98.9)	84/84 (100)	5/6 (83.3)
Radiological test (most advanced)	90/90 (100)	84/84 (100)	6/6 (100)
CT	81/90 (90)	75/84 (89.3)	6/6 (100)
X-ray	6/90 (6.7)	6/84 (7.1)	0/6 (0)
CT/X-ray (not clearly stated)	3/90 (3.3)	3/84 (3.6)	0/6 (0)
BALF cytology	40/90 (44.4)	36/84 (42.9)	4/6 (66.7)
Biopsy	5/90 (5.6)	2/84 (2.4)	3/6 (50)

*Data are n/N (%), where N is the total number of patients with available data reported in the original article.

†These patients also developed partial bowel obstruction because of the parasite infection.

‡No specific cause for constipation or relevant diagnosis was presented in the article.

§For the indicators whose original number was not reported, we recorded the description in the paper. For the indicators whose original number was reported in some studies, the normal range of laboratory findings was considered as follows: white blood cell count (WBC): 4-10 × 10^9/L, C-reactive protein (CRP): <10 mg/L, procalcitonin (PCT): <0.5 μg/L[51-53]. No original number of erythrocyte sedimentation rate (ESR) was reported.

TABLE 4 The treatment and outcome details of the included patients

Feature	n/N (%)*		
	Overall	**sBAL**	**WLL**
Lavage pattern			
sBAL	84/90 (93.3)	–	–
WLL	6/90 (6.7)	–	–
Onset-lavage interval (t_1)			
$t_1 \leq 1$ week	4/24 (16.7)	4/21 (19.0)	0/3 (0)
1 week$< t_1 \leq$1 month	15/24 (62.5)	13/21 (61.9)	2/3 (66.7)
1 month$< t_1 \leq$3 months	3/24 (12.5)	2/21 (9.5)	1/3 (33.3)
3 months$< t_1 \leq$1 year	1/24 (4.2)	1/21 (4.8)	0/3 (0)
$t_1 >$1 year	1/24 (4.2)	1/21 (4.8)	0/3 (0)
Admission-lavage interval (t_2)			
$t_2 \leq$1 week	6/12 (50)	6/8 (75)	0/4 (0)
1 week$< t_2 \leq$1 month	3/12 (25)	1/8 (12.5)	2/4 (50)
1 month$< t_2 \leq$3 months	2/12 (16.7)	0/8 (0)	2/4 (50)
3 months$< t_2 \leq$1 year	1/12 (8.3)	1/8 (12.5)	0/4 (0)
$t_2 >$1 year	0/12 (0)	0/8 (0)	0/4 (0)
Times of lavage			
1	30/39 (76.9)	25/33 (75.8)	5/6 (83.3)
2	1/39 (2.6)	0/33 (0)	1/6 (16.7)
3-5	7/39 (17.9)	7/33 (21.2)	0/6 (0)
6 and more	1/39 (2.6)	1/33 (3.0)	0/6 (0)
Volume (V)			
V≤100 ml	1/72 (1.4)	1/68 (1.5)	0/4 (0)
100 ml <V≤500 ml	31/72 (43.1)	31/68 (45.6)	0/4 (0)
500 ml <V≤2000 ml	4/72 (5.6)	3/68 (4.4)	1/4 (25)
V> 5 L	3/72 (4.2)	0/68 (0)	3/4 (75)
Weight-dependent	33/72 (45.8)	33/68 (48.5)	0/4 (0)
Lavage Fluid†			
Normal saline	88/90 (97.8)	83/84 (98.8)	5/6 (83.3)
Other fluids	2/90 (2.2)	1/84 (1.2)	1/6 (16.7)
Other reported important therapies			
Antibiotics	30/63 (47.6)	30/58 (51.7)	0/5 (0)
Corticosteroids	5/63 (7.9)	3/58 (5.2)	2/5 (40)
Antibiotics + Corticosteroids	28/63 (44.4)	25/58 (43.1)	3/5 (60)
Main outcomes			
Clinical improvement	87/90 (96.7)	82/84 (97.6)	5/6 (83.3)
In-hospital death	3/90 (3.3)	2/84 (2.4)	1/6 (16.7)
Follow-up recurrence	1/29 (3.4)	1/26 (3.8)	0/3 (0)
Radiological change			
Full resolution	41/72 (56.9)	40/67 (59.7)	1/5 (20)
Partial resolution	31/72 (43.1)	27/67 (40.3)	4/5 (80)
Lung function			
Full improvement	10/10 (100)	9/10 (90)	1/10 (10)

*Data are n/N (%), where N is the total number of patients with available data reported in the original article.

†Because normal saline was a routine lavage fluid, for the studies in which the lavage fluid was not directly described, we documented the normal saline as the lavage fluid in data extraction.

normal gas-exchange and initiate lung fibrotic process. Based on similar mechanisms, therapeutic lung lavage might be potentially effective for ELP.

The application of therapeutic lung lavage in ELP has been rising. In ELP, the lipid substances aspirated or inhaled into the lungs might be absorbed by macrophages, which cannot metabolize them, while some lipid substances might be floating extracellularly in the alveoli.[55,64] The chronic inflammatory response is often mediated by the activated macrophages, which may lead to pulmonary fibrosis.[65] Therapeutic lung lavages have the potential to help remove the lipid substances, lipid-laden macrophages, and inflammatory factors, thus delaying the progress in the development of interstitial fibrosis.[66] WLL and sBAL are both used in clinical settings. In current literature, sBAL has much more widespread application in patients, probably because sBAL is safer and more convenient than WLL. In the reported data, patients receiving WLL have higher proportion of cough, dyspnea, and respiratory failure and most patients receiving WLL are adults. In a case report, the physicians intended to treat a 2-year-old infant with WLL at first but applied segmental lavage eventually because the patient could not maintain satisfying oxygen saturation during the WLL procedure.[31] Thus, as it is a high-risk intervention, WLL is more likely to be applied to patients with well tolerability, and severe or lasting diseases which the phycisians consider cannot be solved by sBAL. As for the lavage fluid, the most popular one is the normal saline, in line with the usual practice in diagnostic bronchoalveolar lavage. However, as lipid's solubility in normal saline is relatively low, Russo et al. tried several fluids in vitro and finally used a solution of 0.05% polysorbate 80 in Ringer's lactate in the lavage and the patient was cured.[43] Normal saline might not be the ideal lavage fluid for ELP. However, due to safety concern, it is still the most widely used lavage fluid. Further studies are needed to find the solution with the best efficacy and safety for lavage in ELP.

We also concluded two characteristics which was reported with low frequency in the literature, the onset-lavage interval and admission-lavage interval. As the progress of the interstitial fibrosis initiated by lipid substances is hard to be reversed, it is essential to promote the clearance of lipid substances as early as possible.[22,23] Thus, the lavage interval time might influence the therapy response of the patients. The rate of reporting the exact lavage time is very low. In patients with reported data, most patients received lung lavage from 1 week to 1 month after the onset of symptoms. The reason might be patients' delay in seeking medical care. The long interval between admission to lavage might be because of delay in diagnosis and the attempt for other therapies. The possible delay of diagnosis in many ELP patients highlight the importance of a complete medical history inquiry. Timely identification of exposure history to lipid combined with key clinical findings may lead to an early diagnosis of ELP. In terms of co-therapies, corticosteroids are reported effective in some studies as it has the potential to inhibit the inflammatory response in the lungs.[5] In fact, corticosteroids work as co-therapy in many included case reports and case series during patients' hospitalization or follow-up, and no comparison groups are set. Therefore, it is hard to evaluate the role of lung lavage. In some case reports, the lung lavage is applied after the physicians consider the corticosteroid therapy had no responses, where the efficacy of lung lavage can be more evident. Most of the reported patients clinically improved, and only 3.3% of the patients deteriorated and eventually died, indicating the possible short-term efficacy of therapeutic lung lavage. Besides, most patients with follow-up data remained well without use of any drugs, revealing the potential long-term efficacy of therapeutic lung lavage. However, there was no commonly accepted definition of clinical improvement and no control arm in the studies, and the long-term follow-up data were often not well presented. Therefore, the actual short-term and long-term efficacy of lung lavage remains to be explored.

For diseases with low incidence and research resources such as ELP, case reports and case series studies become essential sources of clinical evidence.[11,67,68] However, in this review, we find that some important information is not reported in the included studies. The rate of "unknown" data in many items range from 5.6% to 100%. The detailed percentage of the data taking the unknown part into account is described in Tables S3 and S4. Given the unsatisfactory reporting status and relatively low methodological quality of current case reports and case series studies about ELP, we conclude a recommended reporting item list for case reports and case series studies related to therapeutic lung lavage in ELP patients. The list is established based on the reporting status of the included studies, and we recommend relevant case reports to meet the criteria of both this item list and the CARE guideline.[69] The recommended important information to report has the following sections: General information, Clinical findings, Lung lavage, Other treatments, Outcomes and follow-up (Table 5).

This review has several limitations. The most significant limitation is the type of included studies. There are only case reports and case series studies available. Thus, only qualitative summary of current data can be performed, and publication bias may exist. The included studies have relatively high risk of bias and there are many confounders such as co-treatments (eg, corticosteroids, antibiotics, etc.), making it hard to infer the actual role of therapeutic lung lavage in the recovery of the patients. Besides, the reporting of many necessary items is missing. Thus, when calculating the percentage in the tables, we use the number of patients in whom an item is reported but not the overall number of included patients as the denominator. The percentage including the patients with missing data into the denominator is reported in Tables S3 and S4. Also, the heterogeneity of reporting is high and the

TABLE 5 Recommended report item list for case reports and case series studies related to therapeutic lung lavage for ELP

Sections and items	No.
General information	
Demographic information	1
The type of aspirated lipid substance	2
Medical history and underlying diseases (exact description of time)	3
Clinical findings	
Main symptoms/signs and the duration of the symptoms/signs	4
Relevant physical examination findings	5
Laboratory testing, such as ABG, blood routine, CRP, PCT and ESR, both before and after the treatment	6
Microbiological findings from respiratory specimens (eg, sputum, bronchoalveolar lavage)	7
Radiological findings (CT is recommended)	8
Bronchoalveolar cytology (or the cytology of other respiratory specimens)	9
The pathological result of lung biopsy (If a biopsy is performed)	10
Clearly stated important negative clinical findings	11
Therapeutic lung lavage	
The type of lung lavage (sBAL or WLL)	12
The fluid used in the lavage and its volume	13
Times of lavage	14
The interval between symptom onset to lavage	15
The interval between admission to lavage	16
Other treatments	
• An explicit description of other therapies such as corticosteroids and antibiotics, with specific administration information (dosage, duration) and any change in the treatment (exact time and reason) • It should be clearly described if there is no other treatment.	17
Outcomes and follow-up	
Descriptions of the outcomes in all follow-up visits, recommended outcomes include: • Clinical improvement • Radiological improvement • Lung function • Patient safety (adverse events) • Quality of life (if available)	18
The treatments (eg, drugs, lung rehabilitation) applied in the follow-up period with details (eg, dosage and duration for drugs).	19
For case series studies, a summary table of the above information (aggregated level) as well as an in-detail report of each patient (individual level) is recommended.	
The individual characteristics of each patient in the case series (Given the word limit of the main manuscript, the individual characteristics may be described in the online supplementary materials.)	20

reporting is often unclear or ambiguous. Although we tried to define ambiguous items as clearly as possible (Table S2), there might be bias in data extraction.

5 | CONCLUSIONS

In summary, this systematic review suggests that therapeutic lung lavage has the potential to be an effective and safe treatment with long-term benefits for ELP. However, current studies were all case reports and case series with relatively high risk of bias. Prospective clinical studies such as randomized controlled studies, or multicenter registry studies are needed to explore the actual efficacy (short-term/long-term), safety, individualized indications, and optimized treatment procedure of therapeutic lung lavage (eg, timing of treatment, type of lavage fluid, etc.).

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

C. Wang and B. Cao designed the review. L. Shang, X. Gu, S. Du, Y. Wang, B. Cao, and C. Wang finished the protocol. L. Shang and X. Gu performed the literature search and

retrieved articles, L. Shang, S. Du, and X. Gu performed the literature screening, data extraction, and quality assessment. L. Shang, X. Gu, S. Du, Y. Wang, B. Cao, and C. Wang contributed to analysis and interpretation of the data. L. Shang and X. Gu drafted the manuscript. C. Wang, B. Cao, Y. Wang, and S. Du revised the manuscripts. All authors approved the manuscript.

DATA AVAILABILITY STATEMENT

This systematic review performs qualitative descriptions of current studies but not quantitative synthesis (meta-analysis). Thus, data sharing is not applicable to this review as no new data were created or analyzed in this review.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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