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TITLE:
Complementary and alternative medicine for the treatment of bronchiolitis in infants: A systematic review

ABSTRACT:
BACKGROUND: Bronchiolitis is a common cause of hospitalization among infants. The limited effectiveness of conventional medication has prompted the use of complementary and alternative medicine (CAM) as alternative or adjunctive therapy for the management of bronchiolitis. AIMS: To determine the effectiveness and safety of CAM for the treatment of bronchiolitis in infants aged less than 2 years. METHODS: A systematic electronic search was performed in Medline, Embase, CINAHL, AMED, and Cochrane Central Register of Controlled Trials (CENTRAL) from their respective inception to June 30, 2016 for studies evaluating CAM as an intervention to treat bronchiolitis in infants (1 month to 2 years of age). The CAM could be any form of treatment defined by the National Center for Complementary and Integrative Health (NCCIH) and was utilized either as a single agent or adjunctive therapy. The predefined primary outcome was length of hospital stay. Secondary outcomes were time to resolution of bronchiolitis symptoms, adverse events, and all other clinical outcomes reported by the included studies. RESULTS: The review identified 11 studies (8 randomized controlled trials and 3 cohort studies) examining four herbal preparations and four supplements used either as adjunctive or alternative therapy for bronchiolitis in 904 infants. Most studies were of moderate quality. Among six studies reporting on length of stay, a significant benefit was found for Chinese herbal medicine compared to ribavirin in one cohort study (n = 66) and vitamin D compared to placebo in one randomized controlled trial (n = 89). Studies of Chinese herbal medicine (4 studies, n = 365), vitamin D (1 study, n = 89), N-acetylcysteine (1 study, n = 100), and magnesium (2 studies, n = 176) showed some benefits with respect to clinical severity scores, oxygen saturation, and other symptoms, although data were sparse for any single intervention and the outcomes assessed and reported varied across studies. Only five studies reported on adverse events; no serious adverse events were reported. CONCLUSIONS: Among 11 studies examining the effect of CAM on inpatients with bronchiolitis, six reported on the review's primary outcome of length of hospital stay. In general, findings did not show a significant benefit associated with the primary outcome. Preliminary evidence indicated that Chinese herbal medicine mixtures, vitamin D, N-acetylcysteine, and magnesium might be useful in managing the symptoms of bronchiolitis. However, the evidence was not sufficient or rigorous enough to formulate recommendations for the use of any CAM. Among studies that reported adverse events, no serious harms were noted.

Introduction:
Bronchiolitis is the most common acute lower respiratory tract infection of viral origin among infants [1]. It is characterized by cough, rhinorrhea, crackles, wheezes, fever, and hypoxemia [2–4]. Common etiology includes respiratory syncytial virus, rhinovirus, adenovirus, coronavirus, human metapneumovirus, influenza, or parainfluenza [5, 6]. The economic and social implications of bronchiolitis are substantial. In North America, hospitalizations attributable to bronchiolitis have increased twofold over the past two decades [7, 8]. The disease currently accounts for more than 100 thousand hospital admissions annually at an estimated cost of $1.73 billion [9]. In the United Kingdom, 1 in 3 infants will develop bronchiolitis in the first year of life and 2 to 3% of all infants require hospital admissions. In England alone, there were 30,451 secondary care admissions for bronchiolitis between 2011 and 2012 [10].
Despite decades of research, effective pharmacotherapy for bronchiolitis is still lacking. The current treatment is controversial and there are no definitive recommendations for the use of any drug in the routine management of bronchiolitis [6]. Common pharmacological agents such as bronchodilator, corticosteroid, and hypertonic saline have been shown to only provide symptomatic relief [11]. Maintaining hydration and oxygenation of patient remains the cornerstone of management [12]. In the absence of efficacious curative therapy, the use of complementary and alternative medicine (CAM) in bronchiolitis is gaining popularity [13].
Over the past few years, several studies have examined the effects of different CAMs for bronchiolitis, but making sense of this literature requires a comprehensive and systematic synthesis of the available evidence. The aim of the current study was to comprehensively appraise the effectiveness and safety of CAMs for the treatment of bronchiolitis in infants.

Search strategy and selection criteria ::: Methods:
A comprehensive electronic literature search was carried out in Medline, Embase, CINAHL, AMED, and CENTRAL from inception until June 30, 2016 by one investigator (KPK). The search strategy was constructed using a combination of keywords including “alternative medicine”, “complementary medicine”, “herbal medicine”, herb*, “traditional medicine”, “chinese medicine”, “chinese traditional”, “asian traditional”, “alternative therapy”, “complementary therapy”, “herbal therapy”, “traditional therapy”, supplement*, antioxidant, vitamin, natural, homeopathy, kinesiology, kinesiotherapy, “osteopathic medicine”, “osteopathic manipulation”, and bronchiolitis (S1 Text). This was complemented with additional searches of bibliographies in relevant primary and review articles.
Articles were included if they met the following criteria: (1) randomized controlled trials or prospective cohort studies published in English or Chinese language and available in full-text; (2) investigated the use of any form of complementary and alternative medicine defined by the National Center for Complementary and Integrative Health (NCCIH) as a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine [15] either as a single agent or adjunctive therapy; (3) had a comparison group (either placebo or other therapy); and (4) involved inpatients or outpatients aged one month to two years with clinically diagnosed bronchiolitis [16].

Study selection and data extraction ::: Methods:
Two investigators (KPK and SWHL) independently screened the titles and abstracts. Full texts of relevant articles were retrieved and reviewed independently to determine eligibility for inclusion in the review. Any disagreement was resolved through discussion.
Data regarding study design, participants, interventions, clinical outcomes, and adverse events were independently abstracted by two investigators (KPK and SWHL) using a standardized data collection form. We also contacted five corresponding authors for additional information [17–21] and two responses were received [17, 20].

Study quality assessment ::: Methods:
Two investigators (KPK and SWHL) independently assessed the methodological quality of randomized controlled trials using Cochrane risk of bias assessment tool, which covered seven domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and an auxiliary domain (other bias) [22]. For cohort studies, Newcastle-Ottawa Quality Assessment Scale was used, which evaluated the study methodologies based upon three parameters: selection of participants, comparability of cohorts on the basis of design or analysis, and outcome ascertainment. Disagreements were resolved by consensus between two investigators (KPK and SWHL) [23].

Data analysis ::: Methods:
The predefined primary outcome was length of hospital stay. Secondary outcomes included time to resolution of bronchiolitis symptoms, adverse events, and all other clinical outcomes reported by the included studies such as clinical severity scores, rate of cure, oxygen saturation, bronchiolitis symptomatology presentation over the treatment period, duration of fluid or nutrition replacement, use of oxygen supplementation, and use of respiratory support.
Characteristics and results of all included studies were summarized and tabulated. Descriptive analysis was performed for all studies by both investigators (KPK and SWHL), and the results were presented narratively. Data were extracted to calculate relative risk (RR) for dichotomous outcomes or mean difference (MD) for continuous outcomes and their associated 95% confidence intervals (CIs) and p-values with a random effects model using Review Manager (RevMan) software, version 5.3. For studies that reported the data as medians, the respective median values and p-values were presented accordingly. A probability of ≤ 0.05 was considered statistically significant [24–27]. A meta-analysis was not performed due to the variability in the different outcomes assessed, study designs, and CAM interventions used.

Study characteristics ::: Results:
Our initial search yielded 1,220 studies, of which 31 underwent full-text evaluation and 11 unique studies were included in this review (Fig 1). They comprised 8 randomized controlled trials [17–21, 28–30] and 3 cohort studies [31–33] conducted in Asia, enrolling a total of 904 inpatient infants

presenting with bronchiolitis. Sample size of the studies varied between 24 and 133 participants, with age ranging from 1 to 24 months. The studies were published between 1997 and 2015 in English (n = 9) [17–21, 28–30, 32] and Chinese (n = 2) [31, 33] language. Four studies were multicenter [17, 18, 28, 30] and seven were single-center [19–21, 29, 31–33]. Study duration ranged from one day to one week. In all studies, bronchiolitis was diagnosed by a physician based on symptoms of acute wheezing or respiratory distress. In seven studies, the infants were diagnosed as first time wheezers [17–19, 21, 28–30]. Another one study recruited a combination of wheezing and non-wheezing patients [20]. No specific information was provided in three studies [31–33] (Table 1). Three studies were funded by university or government agencies [18, 28, 30], whilst the other eight studies had no sponsorship [17, 19–21, 29, 31–33]. The main characteristics and results of included studies were summarized in Tables 2 and 3.

Interventions ::: Results:
Four herbal preparations [30–33] and four supplements [17–21, 28, 29] were examined. They included Chinese herbal medicine (3 herbal mixtures [31–33] and 1 herbal monopreparation [30]), vitamin D [29], N-acetylcysteine [17], zinc [18–20], and magnesium [21, 28]. Five studies compared placebo to treatment [18–20, 29, 30], whilst another six studies had active comparators such as ribavirin [31], salbutamol [17, 21], epinephrine [28], conventional care (cephalosporins, aminophylline, and oxygen) [33], or Chinese herbal medicine Xiao Er Ke Chuan Ling [32]. The most commonly reported outcomes were duration of hospital stay (n = 6 studies) [17, 19, 21, 28, 29, 31], time to symptom resolution (n = 6 studies) [18–20, 29, 31, 33], cure rate (n = 3 studies) [31–33], and clinical severity scores during hospitalization (n = 4 studies) [17, 21, 28, 30].

Randomized controlled trials ::: Study quality assessment ::: Results:
The methodological quality of the 8 randomized controlled trials (RCTs) was generally moderate. Three trials had all domains judged as low risk of bias [20, 28, 30]. Most trials had an appropriate method of randomization as well as allocation concealment. Seven studies mentioned double blinding, of which only three described details of blinding of patients, personnel, and outcome assessors [20, 28, 30]. All studies were judged to have sufficient reporting of outcomes and have low risk of bias of selective outcome reporting. However, all studies had an unclear risk of other source of bias (Fig 2).

Cohort studies ::: Study quality assessment ::: Results:
The observational study by Feng and colleagues lacked methodological details for quality assessment [32]. The other two studies generally had a good quality of cohort selection and comparability, but, independent blind outcome assessment and adequacy of follow up were not described [31, 33].

Chinese herbal medicine ::: Effects of complementary and alternative medicine in bronchiolitis ::: Results:
Four different preparations of Chinese herbal medicine were examined. The herbal composition and medicinal properties of the respective Chinese herbal medicine are described in S1 Table. The mechanism of action for each herbal medicine is presented in S2 Table.

Shuang Huang Lian ::: Effects of complementary and alternative medicine in bronchiolitis ::: Results:
In the cohort study by Wang et al. (n = 66), the authors examined the use of Shuang Huang Lian injection and found a significant decrease in the length of hospital stay (MD: -1.78 days, 95% CI: -2.72 to -0.84; $p<0.01$) and duration of pulmonary signs of bronchiolitis (MD: -1.88 days, 95% CI: -2.60 to -1.16; $p<0.01$) compared with patients receiving ribavirin [31]. The study also examined other outcomes as shown in Table 2.

Laggera pterodonta ::: Effects of complementary and alternative medicine in bronchiolitis ::: Results:
The randomized trial examining Laggera pterodonta did not assess for duration of hospitalization. The study (n = 133) showed that 97% of patients were eligible for discharge on the third day of admission compared to 76% in the placebo group (RR: 1.28, 95% CI: 1.11 to 1.48; $p<0.01$). The study also showed a significantly lower clinical severity score throughout hospital stay among the patients receiving Laggera pterodonta (effect estimates were not calculated due to the lack of data in the original study) [30]. The study also examined other outcomes as shown in Table 2.

Ephedra-containing herbal decoction ::: Effects of complementary and alternative medicine in bronchiolitis ::: Results:
The following two studies did not evaluate the outcome of hospital length of stay.
In the first cohort study by Feng et al. (n = 75), the authors found 54% higher cure rate in patients administered the oral liquid Jie Jing Ding Chuan Zhi Xiao Tang formulation (RR: 5.00, 95% CI: 1.96 to 12.74; p<0.01) [32].
The other cohort study (n = 91) examined the effects of inhaled Xiao Er Zhi Chuan Tang as an adjuvant to usual care. The herbal formulation was found to shorten the duration of respiratory symptoms such as cough (MD: -2.30 days; 95% CI: -3.02 to -1.58; p<0.01), fever (MD: -1.60 days; 95% CI: -2.14 to -1.06; p<0.01), dyspnea (MD: -2.50 days, 95% CI: -3.02 to -1.98; p<0.01), chest wall retraction (MD: -1.60 days, 95% CI: -1.95 to -1.25; p<0.01), rales (MD: -2.00 days, 95% CI: -2.66 to -1.34; p<0.01), and wheezing (MD: -1.90 days, 95% CI: -2.60 to -1.20; p<0.01) and result in 20% higher cure rate (RR: 1.26, 95% CI: 1.03 to 1.54; p = 0.03) compared to conventional treatment [33]. The study also examined other outcomes as shown in Table 2.

Supplements ::: Effects of complementary and alternative medicine in bronchiolitis ::: Results:
The mechanism of action for each supplement is shown in S2 Table.

Vitamin D ::: Effects of complementary and alternative medicine in bronchiolitis ::: Results:
One randomized trial (n = 89) examined the effects of vitamin D supplementation in bronchiolitis. The authors found vitamin D was more effective than placebo in reducing hospital length of stay (MD: -59.00 hours, 95% CI: -63.66 to -54.34; p<0.01), duration of bronchiolitis symptoms (MD: -49.00 hours, 95% CI: -53.25 to -44.75; p<0.01), and duration of feeding problem (MD: -16.00 hours, 95% CI: -17.47 to -14.53; p<0.01) [29]. The study also examined other outcomes as shown in Table 3.

N-acetylcysteine ::: Effects of complementary and alternative medicine in bronchiolitis ::: Results:
In the randomized trial (n = 100) by Naz and colleagues, N-acetylcysteine showed no significant benefit in length of hospital stay (MD: -0.62 days, 95% CI: -1.48 to 0.24; p = 0.16) compared to salbutamol. Patients receiving N- acetylcysteine showed better improvement in clinical severity score than those receiving salbutamol (MD: -1.72, 95% CI: -1.87 to -1.57; p<0.0001) [17].

Zinc ::: Effects of complementary and alternative medicine in bronchiolitis ::: Results:
In a randomized trial (n = 100) conducted by Gupta and collaborators, oral zinc was reported to have no beneficial effect in the outcome of length of hospital stay [19]. Together with two other trials, zinc showed no benefit in managing clinical symptoms of bronchiolitis (Table 3) [18–20]. The latter two studies did not assess for the outcome of length of hospital stay.

Magnesium ::: Effects of complementary and alternative medicine in bronchiolitis ::: Results:
Two studies evaluated magnesium, either alone or as an adjuvant therapy for bronchiolitis in infants. The study by Modaresi and co-workers (n = 120) found no significant difference in duration of hospitalization (MD: -0.40, 95% CI: -3.94 to 3.14; p = 0.82) between magnesium-treated patients and conventional treatment group. However, magnesium treatment was associated with significantly better improvement in clinical severity scores compared to epinephrine (Table 3) [28].
In a three-arm randomized trial by Kose et al. (n = 56), no significant difference was observed in the duration of hospitalization between the groups (20 (magnesium/salbutamol) vs. 24 (magnesium) vs. 24 hours (salbutamol); p>0.05). Inhalation of magnesium and salbutamol combination resulted in lower clinical severity scores compared to those treated with salbutamol (MD: -0.60, 95% CI: -1.18 to -0.02; p = 0.04) or magnesium alone (MD: -1.30, 95% CI: -1.94 to -0.66; p<0.01) [21].

Adverse events ::: Effects of complementary and alternative medicine in bronchiolitis ::: Results:
Five of the total eleven studies provided information on adverse events (AE) [17, 19, 21, 29, 30]. Kose et al. reported no AE such as hypotension, arrhythmias, and loss of deep tendon reflexes in patients treated with inhaled magnesium sulfate monotherapy, salbutamol monotherapy, and salbutamol/magnesium sulfate combination therapy [21]. Likewise, Naz et al. noted that patients treated with inhaled N-acetylcysteine experienced no side effects, including stomatitis, rhinorrhea, nausea, and gastrointestinal disturbances [17]. Two studies examining oral Laggera pterodonta

mixture [30] and oral zinc suspension [19] reported higher incidence of vomiting and diarrhea in the placebo group. The other one study reported no difference in the incidence of diarrhea between infants receiving oral vitamin D drops and placebo [29].

Strengths and limitations ::: Discussion:
The strengths of this review include literature search using five relevant electronic databases without language restriction. There are several limitations that must be addressed. Most of the studies had shortcomings in their study design and outcome reporting. Moreover, the presence of reporting bias may be a cause for concern as all of the current studies are published in Asia, which has previously been shown to produce a large proportion of studies with positive outcomes [42]. Outcomes reported in the primary studies were not ascertained according to the disease severity, which may have impacted the effectiveness outcomes. The study by Deng et al. also compared Chinese herbal medicine with third generation cephalosporins, aminophylline, oxygen, digitalis, or frusemide [33], suggesting the presence of secondary bacterial infection. However, we did not find any evidence of signs and diagnosis of bacterial infection in the article. Furthermore, a large proportion of the included studies (n = 5, 45%) did not report for the primary outcome of interest in this systematic review, albeit they are all inpatient studies. This may be an indication of selective outcome reporting with potential risk of bias.
In addition, publication bias has been recognized as a common phenomenon in clinical literature, in which trials with positive findings have a better chance of being published [43]. As such, any conclusions made exclusively based on published studies can be misleading. The inclusion of only published articles in this review may overestimate the potential benefit of CAM interventions, and thus we urge caution in its interpretation. Another limitation was that the review did not search for grey literature, including conference abstracts, contact with experts and trials registries. As such, we may have missed some studies. In relation to this limitation, we recommend a judicious interpretation of the evidence synthesized in this review as there may be unpublished studies with negative results that we did not include, and thus overestimating the effectiveness of CAM interventions based on the studies that were identified and included. In view of the sparsity of evidence in this area, we recommend that negative and inconclusive as well as positive results should be published or otherwise made publicly available so that the literature can provide evidence base for clinical decision-making. This will facilitate clinicians and patients to understand treatments which are effective, ineffective, safe or even harmful.

Implications ::: Discussion:
It is very likely that more parents will use CAM for their children and this paradigm will continue to rise, particularly in diseases with few therapeutic options available [13, 44]. Current evidence from clinical studies is scarce and often not methodologically robust. Hence, future studies should direct the attention to issues identified in this review, including randomization, blinding, sample size, and complete reporting of safety profiles, particularly, the adverse effects on body systems. Randomized controlled trials would entail closer observation of patients, which would usually translate into better quality of care than would normally occur in the general population. Well-designed randomized controlled trials are considered as the gold standards for judging the benefits of an intervention and would provide the highest level of evidence.
As interest in the potential benefit of CAM grows, it is becoming imperative for healthcare providers to monitor the progress of the clinical literature and to communicate these findings to patients. Until more compelling evidence is available, physicians should remain judicious regarding the use of CAM in bronchiolitis.

Conclusions:
This review identified 11 studies evaluating the effectiveness and safety of a variety of CAM interventions among inpatients with bronchiolitis. Five studies did not examine our primary outcome of hospital length of stay. Four of the remaining six studies did not find a significant benefit associated with the primary outcome. Preliminary evidence indicated that Chinese herbal medicine mixtures, vitamin D, N-acetylcysteine, and magnesium might be potentially useful in managing the symptoms of bronchiolitis. However, the evidence was not sufficient or rigorous enough to formulate recommendations for the use of any CAM. Among studies that reported adverse events, no serious harms were noted. There is a need to conduct more high quality studies to better understand the effectiveness as well as safety of CAM for bronchiolitis in infants.