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PII: S0012-3692(20)30329-9

DOI: https://doi.org/10.1016/j.chest.2020.01.044

Reference: CHEST 2920

To appear in: *CHEST*

Received Date: 20 September 2019

Revised Date: 12 December 2019

Accepted Date: 9 January 2020

Please cite this article as: Smith MP, Lown M, Singh S, Ireland B, Hill AT, Linder JA, Irwin RS, on behalf of the CHEST Expert Cough Panel, Acute Cough Due to Acute Bronchitis in Immunocompetent Adult Outpatients:CHEST Expert Panel Report *CHEST* (2020), doi: https://doi.org/10.1016/j.chest.2020.01.044.

Acute Cough Due to Acute Bronchitis in Immunocompetent Adult Outpatients : CHEST Expert Panel Report

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Conflicts of Interest

There are no conflicts of interest to declare for any of the authors.

Abstract

Background: The evidence for the diagnosis and management of cough due to acute bronchitis in immunocompetent adult outpatients was reviewed as an update to the 2006 American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guideline Cough due to Acute Bronchitis.

Methods:

Acute bronchitis was defined as an acute lower respiratory tract infection manifested predominantly by cough with or without sputum production, lasting no more than 3 weeks with no clinical or any recent radiographic evidence to suggest an alternative explanation. Two clinical PICO (Population, Intervention, Comparison, Outcome) questions were addressed by systematic review in July 2017: firstly, the role of investigations beyond the clinical assessment of patients presenting with suspected acute bronchitis; and secondly, the efficacy and safety of prescribing medication for cough in acute bronchitis. An updated search was undertaken in May 2018.

Results:

No eligible studies relevant to the first question were identified. For the second question, only one relevant study met eligibility criteria. This study found no difference in number of days with cough between patients treated with an antibiotic or an oral non-steroidal anti-inflammatory agent compared with placebo. Clinical suggestions and research recommendations were made based on the consensus opinion of the CHEST Expert Cough Panel.

Conclusion:

The panelists suggested that no routine investigations be ordered and no routine medications be prescribed in immunocompetent adult outpatients first presenting with cough due to suspected acute bronchitis, until such investigations and treatments have been shown to be safe and effective at making cough less severe or resolve sooner. If the cough due to suspected acute bronchitis persists or worsens, a reassessment and consideration of targeted investigations should be considered.

Abbreviations:

PICO: population, intervention, comparison, outcome

ACCP: American College of Chest Physicians

Summary of suggestions

1. For immunocompetent adult outpatients with cough due to suspected acute bronchitis, we suggest no routine investigation with chest x-ray, spirometry, peak flow measurement, sputum for microbial culture, respiratory tract samples for viral PCR, serum C-Reactive Protein (CRP) or procalcitonin. (*Ungraded consensus based statement*).

2. For immunocompetent adult outpatients with cough due to suspected acute bronchitis, to help establish the etiology if the acute bronchitis persists or worsens, we suggest that the patient is advised to seek reassessment and targeted investigation(s) be considered. (*Ungraded consensus based statement*).

   Remarks: Suggested targeted investigations could include chest x-ray, sputum for microbial culture, peak expiratory flow rate recording(s), complete blood count and inflammatory markers such as CRP.

3. For immunocompetent adult outpatients with cough due to acute bronchitis, we suggest no routine prescription of antibiotic therapy, antiviral therapy, antitussives, inhaled beta agonists, inhaled anticholinergics, inhaled corticosteroids, oral corticosteroids, oral NSAIDs or other therapies until such treatments have been shown to be safe and effective at making cough less severe or resolve sooner. (*Ungraded consensus based statement*).

4. For immunocompetent adult outpatients with cough due to acute bronchitis, if the acute bronchitis worsens, we suggest consideration for treatment with antibiotic therapy if a complicating bacterial infection is thought likely. (*Ungraded consensus based statement*).

Remarks: Differential diagnoses, such as exacerbations of chronic airways diseases (chronic obstructive pulmonary disease, asthma, bronchiectasis) that may require other therapeutic management (such as with oral corticosteroids) should also be considered.

Background

Acute bronchitis, manifested by an acute cough and referring to inflammation of the trachea and lower airways, is a common clinical condition responsible for both primary care consultations and emergency department attendances.[1]

Currently, the diagnosis is clinical, with the importance of initial assessment being the exclusion of pertinent differential diagnoses. The CHEST 2006 Guideline recommended that acute bronchitis be diagnosed only if there was no evidence of pneumonia, the common cold, acute asthma or an exacerbation of chronic obstructive pulmonary disease (COPD).[2]

Previous retrospective cohort studies including patients with a diagnosis of acute bronchitis have found that at initial presentation just over one-third would also meet the criteria for a diagnosis of asthma and that 3 years following a diagnosis of acute bronchitis 34% of the cohort fulfilled criteria for either asthma or chronic bronchitis.[3,4] The initial clinical evaluation is important in the longitudinal care of patients; in a retrospective study of 46 patients with a history of at least 2 similar physician-diagnosed episodes of acute bronchitis, 65% episodes were found to have mild asthma.[5] Presentation with cough due to suspected acute bronchitis warrants a detailed review and exploration of pre-existing health conditions, exposure history and consideration of such differential diagnoses such as the common cold, cough variant asthma, acute exacerbation of chronic bronchitis in a smoker, acute exacerbation of bronchiectasis and acute rhinosinusitis.

Despite this, to date, it is not known whether there is additional value in the routine ordering of investigations such as chest radiographs, sputum cultures, measurement of serum inflammatory markers or indeed other laboratory tests at initial presentation.

Acute bronchitis is considered to be a self-limiting condition but there remains data to suggest that practitioners frequently prescribe both antibiotics and other medication.[6,7] The importance of antimicrobial stewardship is well recognized, as is the individual morbidity experienced from cough due to acute bronchitis, such as days off work and primary care consultations.[8] There is a need to review the evidence for the benefit of routine prescriptions for cough due to acute bronchitis.

The 2006 guideline encompassed both adult and pediatric patients and found no role for sputum cultures, viral or serologic assays in making the diagnosis of acute bronchitis but emphasized the importance of clinically and radiographically excluding other differential explanations for the presentation. The guideline found no role for routine antibiotic use or

mucokinetic agents, but suggested that in adults with accompanying wheeze, inhaled bronchodilator therapy may be useful.

This document sought to update the 2006 guideline, reviewing the role of investigations in the diagnosis of acute bronchitis as well as the efficacy for medications in the management of cough due to acute bronchitis in immunocompetent adult patients.[2] The suggestions made are intended to be useful for clinical practitioners assessing immunocompetent adult patients with cough due to suspected acute bronchitis, both in primary care and emergency departments.

Methods

The methodology of the CHEST Guideline Oversight Committee was used to select the Expert Cough Panel Chair and the international panel of experts in Acute Bronchitis to identify, evaluate and synthesize the relevant evidence and to develop the suggestions that are contained within this article. In addition to the quality of the evidence, the recommendation/suggestion grading also includes strength of recommendation dimension, used for all CHEST Guidelines. The strength of recommendation here is based on consideration of three factors: balance of benefits to harms, patient values and preferences, and resource considerations. Further details of the methods for guideline development including management of conflicts of interests and transparency for all CHEST guidelines have been previously published.[9]

Key Question Development

Key clinical questions (KQ) were developed using the PICO (Population, Intervention, Comparator, Outcome) format. The following two questions were addressed:

Key clinical question (PICO) 1 - For immunocompetent adult outpatients with cough due to suspected acute bronchitis, is there added predictive value over history and physical examination alone from the addition of chest x-ray, spirometry, peak flow measurement, sputum for microbial culture, respiratory tract samples for viral PCR, serum C Reactive Protein or procalcitonin to rule out pneumonia, influenza, pertussis, asthma or acute exacerbation of chronic bronchitis?

Key clinical question (PICO) 2 - For immunocompetent adult outpatients with cough due to acute bronchitis, what are the comparative effectiveness and safety of antibiotic therapy, antiviral therapy, antitussives, inhaled beta agonists, inhaled anticholinergics, inhaled corticosteroids, oral corticosteroids, oral NSAIDs or other therapies on cough and need for additional treatment?

We defined acute bronchitis as:

An acute lower respiratory infection manifested predominantly by cough with or without sputum production, lasting no more than 3 weeks but with no clinical (e.g., heart rate ≥ 100 beats/min, respiratory rate ≥ 30 breaths/min, oral temperature ≥ 37.8 degrees C., and chest examination findings of adventitious sounds) or any recent radiographic evidence to suggest pneumonia and no other alternative explanation [e.g. non-infective causes of cough, sinusitis, exacerbation of an underlying lower respiratory condition such as asthma, bronchiectasis or chronic obstructive pulmonary disease (COPD)].

See Table 1 for the inclusion criteria for each question.

Protocol

The systematic review was registered with PROSPERO – the international prospective register of systematic reviews and can be accessed here: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=78153

Systematic Literature Search

Education and Clinical Services Librarian, Nancy Harger MLS, working in the University of Massachusetts Medical School Library, performed all systematic literature searches for each PICO question in the following databases: PubMed, Scopus, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. The date limitations were from database inception through 08/07/17 for PICO 1 and 07/17/17 for PICO 2. Searches were restricted to English language. Search strategies for PICO 1 and 2 are presented in Appendix A. After completion of the systematic review, an updated search in PubMed alone was conducted on 05/16/18 for both PICO questions using the same search strategies to see if new studies were available.

To achieve dual review, four panelists were divided into two pairs and the retrieval divided in half. Panelists independently reviewed the titles and abstracts of their assigned search results to identify potentially relevant articles based on the inclusion criteria specified in Table 1. Discrepancies were resolved by discussion. Studies determined to be eligible based on abstract review underwent a second round of full-text screening for final inclusion. Important data from each included study were then extracted into structured evidence

tables. In each step, dual review and dual extraction were performed and resolved by discussion.

Quality assessment

All included studies were then subject to quality assessment by the methodologist (B.I.). Systematic reviews were assessed using the Documentation and Appraisal Review Tool (DART).[10] Randomized Controlled Trials were assessed using the Cochrane Risk of bias tool.[11] Observational studies were assessed using the Cochrane Bias Methods Group's Tool to Assess Risk of Bias in Cohort Studies.[12] Diagnostic studies were evaluated using the Modified QUADAS Form for Diagnostic Studies.[13] Studies at high risk of bias or of poor quality were excluded.

Grading the Evidence and Development of Recommendations

When possible, GRADE Evidence Profiles were created to grade the overall quality of the body of evidence supporting the outcomes for each intervention based on five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. The quality of the evidence for each outcome is rated as high, moderate, or low, modified from GRADE standards.[14]

The panel could draft recommendations for each key clinical question that had sufficient evidence. Recommendations would be graded using the CHEST grading system, which is composed of two parts: the strength of the recommendation (either strong or weak) and a rating of the overall quality of the body of evidence. In the case of weak or insufficient evidence, when guidance was still warranted, a weak suggestion could be developed and either graded 2C or labeled "Ungraded Consensus-Based Statement".[9]

All drafted suggestions were presented to the full panel in an anonymous voting survey to achieve consensus through a modified Delphi technique. Panelists were requested to indicate their level of agreement on each statement, using a 5-point Likert scale.[9] Panelists also had the option to provide open-ended feedback on each statement with suggested edits or general comments. For a suggestion to pass it required at least 75% of the Expert Cough Panel to vote and at least 80% of the votes agree or strongly agree with the

statement. *All of the suggestions presented in this article met these rigorous thresholds and no Expert Cough Panelist was excluded from voting.* A patient representative who had been a member of the Cough Panel provided patient-centered input for this expert panel report and approved of the suggestions contained herein.

Peer Review Process

The manuscript with suggestions went through 2 rounds of review. During the first round, reviewers from the Guidelines Oversight Committee (GOC) of the CHEST Organization reviewed the content and methods of the manuscript for consistency, accuracy and completeness. The manuscript was revised after consideration by the panel of the feedback received from the GOC reviewers and then submitted to the *CHEST* journal for review by a representative from the CHEST Board of Regents, 1 of the 4 CHEST Presidents and journal-identified reviewers. Because none of the suggestions were revised, voting did not need to be undertaken again by the entire panel.

Subsequent Guidelines

Future updates to this guideline will be conducted in accordance with the previously published CHEST methodology.[9,15]

Results

Search results for each PICO question are presented at the beginning of each summary.

PICO Question One.

For immunocompetent adult outpatients with cough due to suspected acute bronchitis, is there added predictive value over history and physical examination alone from the addition of chest x-ray, spirometry, peak flow measurement, sputum for microbial culture, respiratory tract samples for viral PCR, serum C Reactive Protein or procalcitonin to rule out pneumonia, influenza, pertussis, asthma or acute exacerbation of chronic bronchitis?

For PICO 1, the first search of PubMed (including recent unindexed articles and systematic review) identified 242 studies. Scopus search identified 238 studies after duplicates removed. A search of Cochrane systematic reviews found 3 studies after duplicates removed. This totaled 483 studies retrieved. Eight studies out of the 483 proceeded to full text review where no studies were determined to meet all inclusion and exclusion criteria specified by the panel.

The PICO 1 updated search retrieved 9 studies; 7 were pediatric, 1 was not acute bronchitis, and 1 was acute bronchitis but did not meet definition for cough duration. None were eligible. The search summary is presented in a PRISMA flow chart in Figure 1.

Summary of Evidence and Discussion

Our systematic review of the literature retrieved no articles meeting all inclusion criteria to specifically address the PICO question on the added predictive value of chest radiograph, spirometry, peak flow measurement, sputum for microbial culture, respiratory tract samples for viral PCR, serum C Reactive Protein or procalcitonin over history and physical examination alone to rule out pneumonia, influenza, pertussis, asthma or acute exacerbation of chronic bronchitis. Nearly half of the 483 studies were excluded for not meeting study design criteria and almost another half were excluded for ineligible patient populations. Many of the ineligible population studies were excluded for focusing on subjects with conditions like common cold, chronic bronchitis, acute exacerbations of COPD, asthma, pneumonia, and other respiratory conditions or for including children. The

diagnosis of acute bronchitis as an entity in its own right may be clinically challenging but using a robust definition for the diagnosis would be helpful for future randomized controlled studies.

The following represent gaps in knowledge. Defining populations to account for comorbidities such as diabetes mellitus would be of clinical importance to physicians and internationally agreed standards for inclusion criteria such as age for adult population studies would also provide a stronger evidence base from which to draw conclusions. In addition to exploring the predictive value of routine laboratory and other investigations in the diagnosis of cough in acute bronchitis, it would be useful to evaluate the predictive value of the test with the duration and severity of acute bronchitis.

Suggestions

1. **For immunocompetent adult outpatients with cough due to suspected acute bronchitis, we suggest no routine investigation with chest x-ray, spirometry, peak flow measurement, sputum for microbial culture, respiratory tract samples for viral PCR, serum C-Reactive Protein (CRP) or procalcitonin. (*Ungraded consensus based statement*).**

2. **For immunocompetent adult outpatients with cough due to suspected acute bronchitis, to help establish the etiology if the cough due to suspected acute bronchitis persists or worsens, we suggest that the patient is advised to seek reassessment and targeted investigation(s) be considered. (*Ungraded consensus based statement*). REMARKS: Suggested targeted investigations could include chest x-ray, sputum for microbial culture and peak expiratory flow rate(s) complete blood count and inflammatory markers such as CRP.**

PICO Question Two.

For adult outpatients with cough due to acute bronchitis what are the comparative effectiveness and safety of antibiotic therapy, antiviral therapy, antitussives, inhaled beta agonists, inhaled anticholinergics, inhaled corticosteroids, oral corticosteroids, oral NSAIDs or other therapies on cough and need for additional treatment?

For PICO 2, the first search of PubMed (including recent unindexed articles and systematic review) identified 292 studies. Scopus search identified 143 studies after duplicates removed. A search of Cochrane systematic reviews found 28 studies after duplicates removed and 168 unique studies were identified from a search of Cochrane Central. This totaled 631 studies retrieved. Seventy-three studies out of the 631 proceeded to full text review, where only 1 study was determined to meet all inclusion and exclusion criteria specified by the panel.[16] Almost two thirds of the 630 studies excluded were for ineligible patient populations and the rest were almost evenly split between ineligible study design and ineligible interventions. Many of the studies excluded for ineligible population once again focused on subjects with conditions like common cold, chronic bronchitis, acute exacerbations of COPD, asthma, pneumonia, and other respiratory conditions or for including children.

The PICO 2 updated search retrieved no new studies. The search summary is presented in a PRISMA flow chart in Figure 2.

Summary of Evidence and Discussion

Our systematic review of the literature discovered 1 study that met all inclusion criteria to address the PICO question on the comparative effectiveness and safety of antibiotic therapy, antiviral therapy, antitussives, inhaled beta agonists, inhaled anticholinergics, inhaled corticosteroids, oral corticosteroids, oral NSAIDs or other therapies on cough and need for additional treatment in immunocompetent adult outpatients with cough due to acute bronchitis.[16]

This study by Llor et al was a multicenter, single blinded RCT in 416 adults with symptoms of respiratory infection (including cough, colored sputum and at least one of dyspnea, wheezing, chest discomfort or chest pain) for less than 1 week duration who attended primary care centers in Spain.[16] They were randomly assigned to one of three treatment regimens - either ibuprofen 600 mg, amoxicillin-clavulanic acid 500mg/125mg, or placebo 3 times a day for 10 days. The primary outcome was the number of days with frequent cough. Median days with frequent cough were reported for each group as: Ibuprofen – 9

days (95% CI = 8 to 10); Amoxicillin-clavulanic acid - 11 days (95% CI = 10 to 12); Placebo – 11 days (95% CI 8 to 14).

The authors concluded no significant differences were observed in the number of days with cough between patients with uncomplicated acute bronchitis and discolored sputum treated with ibuprofen, amoxicillin-clavulanic acid, or placebo.

This PICO question excluded studies involving the efficacy and safety of herbal and complementary therapies for cough in acute bronchitis. Many of these therapies are not regulated nor considered as therapeutic options by medical providers in many countries.

There is insufficient evidence to confirm or refute the efficacy of prescribed treatments for cough due to acute bronchitis. An obvious gap that came out of this systematic review is that randomized controlled studies of treatments with rigorously defined patient populations of sufficient duration are necessary.

Suggestions:

3. **For immunocompetent adult outpatients with cough due to acute bronchitis, we suggest no routine prescription of antibiotic therapy, antiviral therapy, antitussives, inhaled beta agonists, inhaled anticholinergics, inhaled corticosteroids, oral corticosteroids, oral NSAIDs or other therapies until such treatments have been shown to be safe and effective at making cough less severe or resolve sooner. (*Ungraded consensus based statement*).**

4. **For immunocompetent adult outpatients with cough due to acute bronchitis, if the acute bronchitis worsens, we suggest consideration for treatment with antibiotic therapy if a complicating bacterial infection is thought likely. (*Ungraded consensus based statement*).**

   REMARKS: Differential diagnoses, such as exacerbations of chronic airways diseases (chronic obstructive pulmonary disease, asthma, bronchiectasis) that may require other therapeutic management (such as with oral corticosteroids) should also be considered.

AREAS FOR FUTURE RESEARCH

1. **There is a need for randomized controlled trials in adult patients with cough due to suspected acute bronchitis to assess the potential role for both antibiotic and non-antibiotic treatments. Patients with conditions that may mimic acute bronchitis such as cough variant asthma, acute exacerbations of chronic bronchitis, acute exacerbations of bronchiectasis, bacterial sinusitis and the common cold should be excluded. Until these exclusionary conditions are considered and ruled out, the true frequency of acute bronchitis as a distinct clinical entity will not be known.**

2. **There is a need for studies to routinely use reliable and valid cough outcome measures to assess resolution of episodes of cough due to suspected acute bronchitis.**

Conclusion

For immunocompetent adult outpatients presenting with cough due to suspected acute bronchitis, we suggest no routine investigation. If the cough persists or worsens, we suggest reassessment and consideration of targeted investigations. We suggest no routine prescription of antibiotic therapy, antiviral therapy, antitussives, inhaled beta agonists, inhaled anticholinergics, inhaled corticosteroids, oral corticosteroids, oral NSAIDs or other therapies. If the cough due to suspected acute bronchitis worsens, we suggest reassessment and consideration for treatment with antibiotic therapy if a bacterial infection is thought likely or treatment for other alternative conditions deemed likely.

Acknowledgements

Additional Information: CHEST Expert Panel Collaborator, Mark Rosen, MD, FCCP died July 2, 2019.

Author contributions

All authors contributed to the design and analysis of the study and writing of the manuscript.

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Endorsements: This guideline has been endorsed by the American Association for Respiratory Care (AARC).

Other Contributions: We are grateful to Nancy Harger, MLS, Education and Clinical Services Librarian working in the University of Massachusetts Medical School Library in Worcester, MA who undertook all the searches for the systematic reviews.

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Table 1

PICO Questions and Inclusion Criteria

PICO Question	Study Characteristic	Inclusion Criteria
PICO 1 For adult outpatients with cough due to suspected acute bronchitis*, is there added predictive value over history and physical alone from the addition of CXR, pulmonary function testing, sputum for microbial culture, PCR for virus, C Reactive Protein or procalcitonin to rule out pneumonia, influenza, pertussis, asthma or acute exacerbation of chronic bronchitis?	Study Design	1. Systematic Review (with or without meta-analysis) 2. RCT 3. Retrospective or Prospective Cohort Study 4. Cross-sectional study
	Population	1. Ambulatory or outpatient 2. ≥ 18 years of age 3. Acute bronchitis*
	Intervention	1. Chest x-ray 2. sputum for microbial culture 3. PCR for virus 4. C reactive protein 5. procalcitonin 6. spirometry pre- and post-bronchodilator or methacholine challenge
	Comparator	History and physical alone
	Outcomes	1. Primary Outcomes: Exclusion of pneumonia, influenza, pertussis, asthma or acute exacerbation of chronic bronchitis, sinusitis, COPD, bronchiectasis. Use negative Predictive Value 2. Secondary Outcomes: Other diagnostic accuracy test parameters including positive predictive value, sensitivity, specificity, area under ROC curve
PICO 2 For adult outpatients with cough due to acute bronchitis*, what are the comparative effectiveness and safety of antibiotic therapy, antiviral therapy, antitussives, inhaled beta agonists, anticholinergics, inhaled corticosteroids, oral corticosteroids, NSAIDs or other therapies	Study Design	1. Systematic Review (with or without meta-analysis) 2. RCT 3. Retrospective or Prospective Cohort Study
	Population	1. Ambulatory or outpatient 2. ≥ 18 years of age 3. Acute bronchitis*
	Intervention	1. antibiotics 2. antivirals 3. antitussives 4. phosphodiesterase inhibitors 5. antibody therapies 6. anticholinergics 7. beta-agonists 8. antihistamines 9. cough suppressants 10.decongestants 11.zinc

on cough and need for additional treatment? (Note that the decision was made to exclude alternative therapies without FDA or other regulatory approval.)		12.vitamin c 13.ipratropium bromide 14.NSAIDS 15.acetaminophen 16.corticosteroids 17.mucolytics 18.expectorants 19.theophylline
	Comparator	1. No therapy 2. Placebo 3. Another therapy
	Outcomes	Primary Outcomes: 1. Time to resolution of cough symptoms (includes subjective and objective assessment) 2. Change in quantitative differences in cough (cough frequency, cough scores, cough quality of life, other quantitative outcomes based on cough diary) Secondary Outcomes: 1. Time to resolution of moderate cough symptoms (to be defined using GRACE or other standard) 2. Time to resolution of severe cough symptoms (to be defined using GRACE or other standard) 3. Proportion of patients requiring additional outpatient care office visit 4. Proportion of patients requiring emergency department evaluation. 5. Proportion of patients requiring hospitalization. 6. Proportion of patients later prescribed antibiotics Adverse outcomes from treatment

* An acute lower respiratory infection manifested predominantly by cough with or without sputum production, lasting no more than 3 weeks but with no clinical (e.g., heart rate ≥ 100 beats/min, respiratory rate ≥ 30 breaths/min, oral temperature ≥ 37.8 degrees C., and chest examination findings of adventitious sounds) or radiographic evidence to suggest pneumonia and no other alternative explanation (e.g. non-infective causes of cough - sinusitis, exacerbation of an underlying lower respiratory condition such as asthma, bronchiectasis or COPD).

Figure 1
Acute Bronchitis PICO 1 PRISMA Flow Chart

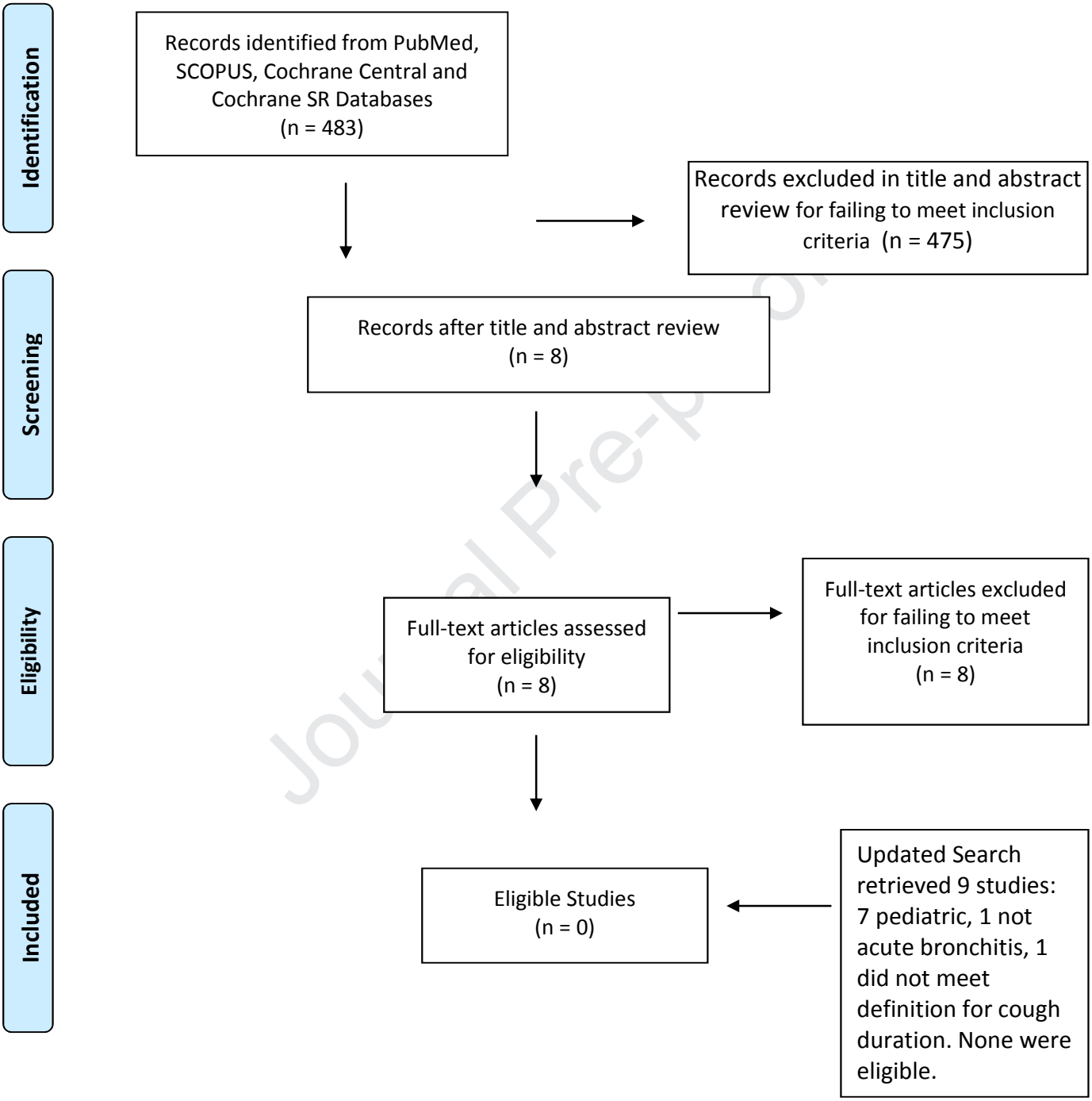

Figure 2
Acute Bronchitis PICO 2 PRISMA Flow Chart