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Adult Outpatients With Acute Cough Due to Suspected Pneumonia or Influenza
CHEST Guideline and Expert Panel Report

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BACKGROUND: Patients commonly present to primary care services with upper and lower respiratory tract infections, and guidelines to help physicians investigate and treat acute cough due to suspected pneumonia and influenza are needed.

METHODS: A systematic search was carried out with eight patient, intervention, comparison, outcome questions related to acute cough due to suspected pneumonia or influenza.

RESULTS: There was a lack of randomized controlled trials in the setting of outpatients presenting with acute cough due to suspected pneumonia or influenza who were not hospitalized. Both clinical suggestions and research recommendations were made on the evidence available and CHEST Expert Cough Panel advice.

CONCLUSIONS: For outpatient adults with acute cough due to suspected pneumonia, we suggest the following clinical symptoms and signs are suggestive of pneumonia: cough; dyspnea; pleural pain; sweating, fevers, or shivers; aches and pains; temperature ≥ 38°C; tachypnea; and new and localizing chest examination signs. Those suspected of having pneumonia should undergo chest radiography to improve diagnostic accuracy. Although the measurement of C-reactive protein levels strengthens both the diagnosis and exclusion of pneumonia, there was no added benefit of measuring procalcitonin levels in this setting. We suggest that there is no need for routine microbiological testing. We suggest the use of empiric antibiotics according to local and national guidelines when pneumonia is suspected in settings in which imaging cannot be performed. Where there is no clinical or radiographic evidence of pneumonia, we do not suggest the routine use of antibiotics. There is insufficient evidence to make recommendations for or against specific nonantibiotic, symptomatic therapies. Finally, for outpatient adults with acute cough and suspected influenza, we suggest that initiating antiviral treatment (according to Centers for Disease Control and Prevention advice) within 48 hours of symptoms could be associated with decreased antibiotic use and hospitalization and improved outcomes. CHEST 2019; 155(1):155-167

KEY WORDS: cough; evidence-based medicine; guidelines; influenza; pneumonia

Summary of Recommendations

1. For outpatient adults with acute cough due to suspected pneumonia, we suggest the following clinical symptoms and signs are suggestive of pneumonia (cough, dyspnea, pleural pain, sweating/fevers/shivers, aches and pains, temperature 38°C or greater, tachypnea and new and localizing chest examination signs) (Ungraded Consensus-Based Statement).

Remarks: The quality of evidence is low, but the absence of runny nose and presence of breathlessness, crackles, and/or diminished breath sounds on auscultation, tachycardia, and fever (38°C or greater) is suggestive of pneumonia.

2. For outpatient adults with acute cough due to suspected pneumonia, we suggest measuring C-reactive protein (CRP) because the addition of CRP to features such as fever (38°C or greater), pleural pain, dyspnea and tachypnoea, and signs on physical examination of the chest (tachypnea and new and localizing chest examination signs) strengthens both the diagnosis and exclusion of pneumonia (Grade 2C).

Remarks: The quality of evidence is low, but a CRP > 30 mg/L in addition to suggestive symptoms and signs increases the likelihood that the cough may be related to having pneumonia. Acute cough (ie, < 3 weeks in duration) is less likely to be caused by a pneumonia when the CRP < 10 mg/L or between 10-50 mg/L in the absence of dyspnea and daily fever.

3. For outpatient adults with acute cough due to suspected pneumonia, we suggest not routinely measuring procalcitonin (Ungraded Consensus-Based Statement).

4. For outpatient adults with acute cough and abnormal vital signs secondary to suspected pneumonia, we suggest ordering a chest radiography to improve diagnostic accuracy (Grade 2C).

5. For outpatient adults with acute cough and suspected pneumonia, we suggest that there is no need for routine microbiological testing (Ungraded Consensus-Based Statement).

Remarks: Microbiologic testing should be considered if the results may result in a change of therapy.

6. For outpatient adults with acute cough, we suggest the use of empiric antibiotics as per local and national guidelines when pneumonia is suspected in settings where imaging cannot be obtained (Ungraded Consensus-Based Statement).

7. For outpatient adults with acute cough and no clinical or radiographic evidence of pneumonia (eg, when vital signs and lung exams are normal) we do not suggest the routine use of antibiotics (Ungraded Consensus-Based Statement).

8. For outpatient adults with acute cough and suspected influenza, we suggest initiating antiviral treatment (as per Centers for Disease Control and Prevention advice) within 48 hours of symptom onset. Antiviral treatment may be associated with decreased antibiotic usage, hospitalization, and improved outcomes (Ungraded Consensus-Based Statement).

Cough is a common presentation to primary care or outpatient services, and cough due to either suspected pneumonia or influenza involves a subset of patients with acute cough who are thought to benefit from disease-specific investigations and therapies. The guideline explored the evidence base for their investigation and management.

Pneumonia and influenza are the eighth leading causes of death overall and the most important death related to infectious diseases in the United States.[1] The overall annual incidence of community-acquired pneumonia (CAP) ranges from 5 to 11 per 1,000 people, with more cases occurring during the winter season.[2,3] In 2006, there were approximately 4.2 million ambulatory care visits for CAP in the United States, and it is estimated that CAP has an annual economic burden that exceeds $17 billion in the United States.[4]

These guidelines refer to patients evaluated in the outpatient setting who present with acute cough (ie, < 3 weeks in duration), accompanied by other symptoms for which the physician suspects pneumonia

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or influenza acquired outside of the hospital setting. The present guidelines specifically refer to a suspected diagnosis of pneumonia and influenza and do not include acute bronchitis and other upper respiratory tract infections. In addition, these guidelines exclude patients who are immunocompromised.

The steering committee developed a series of questions derived from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) format that uses the patient, intervention, comparison, outcome (PICO) question format. Eight PICO questions were formulated, with four addressing the diagnostic confirmation of pneumonia and four focusing on therapeutic strategies that include recommendations on antibacterial treatment, nonantibacterial interventions (eg, short-acting bronchodilators, mucolytics, cough suppressants), and antiviral therapies. Patients with cough and suspected or confirmed pneumonia or influenza who require hospitalization should be treated using guidelines advocated by other organizations addressing those specific clinical conditions.[2,3,5]

Materials and Methods

The methodology of the CHEST Guideline Oversight Committee was used to select the Expert Cough Panel chair and the international panel of experts to perform parts of the systematic review, synthesis of the evidence, and development of the recommendations and suggestions.[6]

Key Question Development

The pneumonia writing group of the CHEST Expert Cough Panel developed eight key clinical questions and a PICO element table. The key questions were as follows:

1. Should chest radiograph plus clinical judgment vs clinical judgment alone be used to guide treatment in outpatients with acute cough to improve patient outcomes?
2. Should C-reactive protein (CRP) or procalcitonin levels rather than symptoms alone be used to predict pneumonia in adult outpatients with acute cough?
3. Should a diagnostic algorithm, clinical prediction rule, or diagnostic score in addition to clinical judgment, compared with clinical judgment alone, be used to confirm the diagnosis of pneumonia in adult outpatients with acute cough?
4. Should microbiological testing in addition to clinical judgment, compared with clinical judgment alone, be used to confirm pneumonia in adult outpatients with acute cough?
5. Should antibiotics rather than no antibiotics be used to treat adult outpatients with acute cough and suspected pneumonia?
6. Should nonantibiotic therapy rather than none be used to treat adult outpatients with acute cough and suspected pneumonia?
7. Should antibiotics with atypical (cover with macrolides or fluoroquinolones) rather than antibiotics without atypical coverage be used to treat adult outpatients with acute cough and suspected pneumonia?
8. Should antiviral therapy rather than no antiviral therapy be used to treat adults with acute cough and suspected or confirmed influenza? Does this reduce antibiotic prescriptions, general practice or primary care visits, ED visits, hospitalizations, or mortality?

See Table 1 for the inclusion criteria for each question.

All systematic searches for each PICO question were performed in the following databases: PubMed, Scopus, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. Searches for all PICO questions were conducted initially in June 2014, and we searched each database from its inception through June 2014. Search for PICO question 8, which was revised slightly, was updated from June 2014 through July 2016. Searches for PICO questions 3, 4, 5, and 6 were rerun in August 2016 (from June 2014 through August 2016), and PICO question 2 was updated in March 2017 (from June 2014 through March 2017). Search diagrams or strings for each PICO question are provided in e-Appendix 1.

Two reviewers for each PICO question independently evaluated the titles and abstracts of the search results to identify potentially relevant articles meeting the inclusion criteria for study design (systematic review with or without meta-analysis, randomized controlled trial [RCT], prospective and retrospective cohort studies, and case studies with 10 or more cases) and adult outpatient populations presenting with acute cough and suspected pneumonia. Identified studies were then obtained and the same two reviewers independently assessed the full text against all inclusion criteria.

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).[7] RCTs were assessed using the Cochrane Risk of bias tool.[8] Diagnostic studies were evaluated using the modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS) form for diagnostic studies; studies at high risk of bias or of poor quality were excluded.[8]

Grading the Evidence and Development of Suggestions

When possible, GRADE evidence profiles were created to grade the overall quality of the body of evidence supporting the outcomes for each intervention on the basis of 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.[9]

The panel drafted recommendations for each key clinical question that had sufficient evidence. Recommendations were graded using the CHEST grading system that 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.[6] In instances in which there was weak evidence, but guidance was still warranted, a weak suggestion was developed and graded 2C. When there was insufficient evidence, suggestions could be developed but are labeled "Ungraded Consensus-Based Statement."[6]

All drafted suggestions were presented to the full panel in an anonymous voting survey to achieve consensus through a modified Delphi technique. The full panel is multidisciplinary, including academic and private practice primary care providers and a consumer representative who provided input from the patients' perspective. Panelists were requested to indicate their level of agreement on each statement by using a 5-point Likert scale.[6] Panelists also had the option to provide open-ended feedback on

TABLE 1] PICO Questions

PICO Question	Study Characteristic	Inclusion Criteria
PICO question 1: chest radiograph plus clinical judgment vs clinical judgment alone	Patient	Adult outpatients with acute cough due to suspected pneumonia
	Intervention	Chest radiograph plus clinical judgment
	Comparison	Clinical judgment alone
	Outcome	Primary outcome: proportion of participants who were not cured or not substantially improved at follow-up
PICO question 2: procalcitonin or CRP levels vs symptoms alone	Patient	Adult outpatients with acute cough due to suspected pneumonia
	Intervention	Procalcitonin or CRP levels plus symptoms
	Comparison	Symptoms alone
	Outcome	Confirmation of pneumonia or rule out
PICO question 3: diagnostic algorithm plus clinical judgment vs clinical judgment alone	Patient	Adult outpatients with acute cough due to suspected pneumonia
	Intervention	Diagnostic algorithm, clinical rule plus clinical judgment
	Comparison	Clinical judgment alone
	Outcome	Confirmation of pneumonia or rule out
PICO question 4: microbiological testing plus clinical judgment vs clinical judgment alone	Patient	Adult outpatients with acute cough due to suspected pneumonia
	Intervention	Microbiological tests such as culture, serologic, and PCR testing
	Comparison	Clinical judgment alone
	Outcome	Confirmation of cause of pneumonia
PICO question 5: antibiotics vs no antibiotics in suspected pneumonia	Patient	Adult outpatients with acute cough due to suspected pneumonia
	Intervention	Antibiotics
	Comparison	No antibiotics
	Outcome	Primary outcome: proportion of participants who were not cured or not substantially improved at follow-up
PICO question 6: nonantibiotic symptomatic treatment plus antibiotic vs antibiotic alone	Patient	Adult outpatients with acute cough due to suspected pneumonia
	Intervention	Cough suppressants, mucolytics, systemic corticosteroids, inhaled corticosteroids, anticholinergics, NSAIDs, vitamins C and D plus antibiotic
	Comparison	Antibiotic
	Outcome	Primary outcome: proportion of participants who were not cured or not substantially improved at follow-up
PICO question 7: antibiotics with atypical coverage vs antibiotics without atypical coverage	Patient	Adult outpatients with acute cough due to suspected pneumonia
	Intervention	Antibiotics with atypical coverage
	Comparison	Antibiotics without atypical coverage
	Outcome	Primary outcome: proportion of participants who were not cured or not substantially improved at follow-up
PICO question 8: antiviral vs no antiviral in suspected pneumonia during influenza season	Patient	Outpatients with acute cough due to suspected pneumonia during influenza season
	Intervention	Antiviral

(Continued)

TABLE 1] *(Continued)*

PICO Question	Study Characteristic	Inclusion Criteria
	Comparison	No antiviral
	Outcome	1. Proportion of patients receiving antibiotic prescription 2. Proportion of patients obtaining outpatient care office visit 3. Proportion of patients receiving ED evaluation 4. Proportion of patients hospitalized 5. Proportion of patients who die 6. Proportion of patients with adverse events (eg, nausea, sleepiness, and so on)

CRP = C-reactive protein; NSAID = nonsteroidal antiinflammatory drug; PCR = polymerase chain reaction; PICO = patient, intervention, comparison, outcome.

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 to 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.

Results

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

PICO Question 1

Should chest radiograph plus clinical judgment vs clinical judgment alone be used to guide treatment in outpatients with acute cough to improve patient outcomes?

Search Results: The search retrieved 43 publications. Abstract and title review identified 19 studies for full-text review. No studies met all criteria.

Summary of Evidence and Discussion: Our literature review disclosed no articles directly addressing this question. Of note, the question is not focused on the diagnostic accuracy of clinical judgment plus a chest radiograph vs clinical judgment alone. Instead, the question is whether adding a chest radiograph to the routine management strategy for patients with acute cough illness leads to improved outcomes. The hypothesis is that the addition of a chest radiograph will lead to better antibiotic and hospitalization decisions that will, in turn, result in improved patient outcomes.

One article partially addressed this PICO question.[10] In this RCT, patients with acute cough all had chest radiographs, but the treating team was randomly assigned as to whether they received the chest radiograph result. If the treating physician thought he or she needed the chest radiograph result, it was provided and the patient was excluded from random assignment. If the physician wanted to order a chest radiograph but did not think it was essential for management, the patient was randomly assigned. In addition, all chest radiographs were reviewed by a separate study physician who could intervene in real time if a significant finding was present. Physicians recorded their treatment plans; then, when randomly assigned to receive chest radiograph results, they could revise their management plan after receiving the chest radiograph result. There were limited patient outcomes available. The yield of chest radiographs was very low in this population, particularly among those for whom the physician did not think he or she needed to order a chest radiograph. Moreover, for the entire randomly assigned population, the provision of chest radiograph results did not lead to better patient outcomes (reduction in length of illness, duration of cough, and duration of sputum production) or significantly different treatment strategies. However, among patients for whom a chest radiograph would not be ordered routinely, approximately 2% had an infiltrate; among those patients, the chest radiograph result led to a higher use of antibiotics and improved clinical outcomes. Thus, the number needed to treat to generate this benefit is very high. The authors concluded that it is safe to not obtain a chest radiograph for all patients with acute cough illness, and they recommended limiting chest radiographs to situations in which the history and physical examination suggest the need for antibiotic treatment and a chest radiograph would alter this decision. So, in a small subset of patients, a chest radiograph provides added diagnostic value in addition to clinical judgment in the management of adults with acute cough.

The search also retrieved a review from the Cochrane Database of Systematic Reviews on chest radiographs for acute lower respiratory tract infections.[11] This review included two RCTs of chest radiographs vs no chest radiographs in acute lower respiratory tract infections in children and adults, one of which is the article cited earlier. Combined, the two RCTs involved 2,024 patients (1,502 adults, 522 children). Populations were heterogeneous, including patients with severe lung disease. The conclusion was that chest radiography did not improve clinical outcomes (duration of illness) for patients with lower respiratory tract infections. Of note, this is a group that is much broader than just patients with acute cough illness.

For adults with acute cough illness, there is insufficient evidence to recommend for or against routinely obtaining a chest radiograph in addition to clinical judgment to make management decisions. A limited number of studies demonstrate that the overall proportion of patients with acute cough illness who have significant radiographic findings is very small; hence, the benefit, if any, of chest radiography for the evaluation of all adults with acute cough illness is likely very small.

Clinical algorithms to identify the subset of patients with a higher risk of underlying pneumonia are needed to help guide the decision to order chest radiographs in this population. See PICO question 3.

PICO Question 2

Should CRP or procalcitonin levels rather than symptoms alone be used to predict pneumonia in adult outpatients with acute cough?

Search Results: The initial search retrieved 41 publications. Abstract and title review identified nine studies for full-text review. Four studies met all criteria. Two primary studies were evaluated by means of the QUADAS tool as meeting standards for fair quality.[12,13] Two systematic reviews were evaluated by means of the DART as meeting quality standards for good quality, but because they included the same studies, only one could be used for evidence without double counting.[14,15] Data were extracted into an evidence table for the three included studies.[12-14]

A new systematic review potentially relevant to the question was discovered during conversation for another related cough guideline article.[16] As a result, an updated search was conducted in March 2017, and 236 publications were retrieved. Abstract and title review identified 10 studies for full-text review, and two studies

met all criteria and were evaluated by means of the DART and the QUADAS tool as meeting standards for good quality.

One of the identified studies was the systematic review, which was newer than the Engel et al[14] review and included many of the same studies. The evidence table was revised to include the studies identified from the initial and updated searches.[16]

Summary of Evidence and Discussion: This summary included three diagnostic studies[12,13,17] and three systematic reviews[14-16] but no interventional studies. The diagnosis of pneumonia was confirmed by using chest radiographs.

Search Results: The study by Steurer et al[13] included 598 patients to explore a decision aid to rule out pneumonia and reduce unnecessary prescriptions of antibiotics in primary care in patients older than 18 years with a new or worsened cough and fever without serious comorbidities. When the CRP levels were < 10 mg/L or if patients with CRP levels between 11 and 50 mg/L did not complain of dyspnea and daily fever associated with cough, no patients had pneumonia.

The study by van Vugt et al[12] included 2,820 patients. The optimal combination of clinical prediction items for the diagnosis of pneumonia included the absence of runny nose and the presence of breathlessness, crackles, and diminished breath sounds at auscultation; tachycardia (> 100 beats per minute); and fever (temperature $\geq 37.8°C$), with a receiver operating characteristic (ROC) curve area of 0.70 (0.65-0.75). Addition of CRP levels at the optimal cutoff > 30 mg/L increased the ROC curve area to 0.77 (0.73-0.81) and improved the diagnostic classification (net reclassification: 28% improvement). In the 1,556 patients classified according to symptoms, signs, and CRP level ≤ 30 mg/L as at low risk (< 2.5%) for pneumonia, the prevalence of pneumonia was 2%. In the 132 patients classified as at high risk (> 20%), the prevalence of pneumonia was 31%. The positive likelihood ratios of low, intermediate, and high risk for pneumonia were 0.4, 1.2, and 8.6, respectively. A simplified diagnostic score based on symptoms, signs, and CRP level > 30 mg/L resulted in proportions of pneumonia of 0.7%, 3.8%, and 18.2% in the low-, intermediate-, and high-risk groups, respectively.

In contrast, the measurement of procalcitonin concentrations added no relevant additional diagnostic information over symptoms and signs. Procalcitonin

concentrations were ≤ 0.25, 0.25 to 0.50, and > 0.50 μg/L in 94%, 3%, and 3% of patients, respectively. The proportions of pneumonia in these groups were 5%, 7%, and 18%, respectively. The addition of continuous procalcitonin to the symptoms and signs model nonsignificantly increased the area under the curve to 0.72 (0.68-0.77; P > .05). The measurement of procalcitonin, therefore, did not lead to additional diagnostic information.

The study by Teepe et al[17] included 3,104 adults with acute cough (≤ 28 days) in primary care settings. The aim of the study was to predict bacterial infection. The study was part of the Genomics to Combat Resistance against Antibiotics in Community-acquired Lower Respiratory Tract Infections in Europe project funded by the Sixth Framework Programme of the European Commission. All patients underwent clinical examination, chest radiography within 7 days of presentation, sputum and nasopharyngeal swabs collected on the day of presentation, and blood drawn for CRP and procalcitonin levels within 24 hours of presentation. Bacterial infection was determined by means of conventional culture, polymerase chain reaction, and serologic testing, and positive results were defined by the presence of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Bordetella pertussis*, or *Legionella pneumophila*. A total of 539 patients (17%) had bacterial lower respiratory tract infection, and 38 (1%) had bacterial pneumonia. The only predictor for lower respiratory tract infection was discolored sputum (area under the ROC curve, 0.56; 95% CI, 0.54-0.59). Adding CRP level > 30 mg/L increased the area under the ROC curve to 0.62 (95% CI, 0.59-0.65). For bacterial pneumonia, comorbidity, fever (temperature ≥ 38°C), and crackles at auscultation had diagnostic value (area under the ROC curve, 0.68; 95% CI, 0.58-0.77). When CRP level > 30 mg/L was added, the area under the ROC curve improved to 0.79 (95% CI, 0.71-0.87). The positive predictive value was 25% (95% CI, 0.6%-80.6%), and the negative predictive value was 99.7% (95% CI, 99.3%-99.9%). Procalcitonin levels did not add diagnostic value (area under the ROC curve, 0.68; 95% CI, 0.58-0.77).

The Falk and Fahey[15] systematic review included 2,194 participants and assessed the diagnostic value of CRP levels in ambulatory care in patients presenting with symptoms suggestive of CAP. CRP levels may be of value in ruling out a diagnosis of CAP in situations in which the probability of CAP is > 10% with a CRP level < 20 mg/L, typically accident victims seen in EDs.

In primary care, because there will be a low test probability of CAP, additional diagnostic testing with CRP levels is unlikely to alter the probability of CAP sufficiently to change subsequent management decisions such as antibiotic prescribing or referral to the hospital.

The Engel et al[14] systematic review in 912 participants evaluated the diagnostic value of CRP levels combined with clinical assessment in patients with lower respiratory tract infection in primary care. Holm et al showed the diagnostic yield for the CRP cutoff point of ≥ 20 mg/L, OR of 5.0 (95% CI, 2.6-9.9), sensitivity of 0.73, specificity of 0.65, positive predictive value of 0.24, and negative predictive value of 0.94. Hopstaken et al showed the diagnostic yield for the CRP cutoff point of ≥ 20 mg/L, OR of 9.9 (95% CI, 2.9-33.7), sensitivity of 0.91, specificity of 0.51, positive predictive value of 0.22, and negative predictive value of 0.97. The two studies showed limited value of CRP level in diagnosing pneumonia, although the diagnostic value increased when CRP measurement was combined with clinical assessment.

The Minnaard et al[16] systematic review in 5,308 patients quantified the added value of CRP measurement in the diagnostic workup for CAP in primary care. The pooled estimate of improvement in the area under the curve for the extended diagnostic prediction model that includes CRP level to discriminate between patients with and those without pneumonia in primary care was 0.075 (95% CI, 0.044-0.107). With use of a model with a low risk threshold (2.5%), pooled sensitivity was 0.97 (95% CI, 0.95-0.98) in both the basic and extended models, and specificity was 0.28 (95% CI, 0.27-0.29) for the basic and 0.36 (95% CI, 0.34-0.37) for the extended model. At the high risk threshold (20%), pooled sensitivities were 0.63 (95% CI, 0.59-0.66) for the basic and 0.70 (95% CI, 0.66-0.73) for the extended model. Specificities were 0.87 (95% CI, 0.86-0.88) for the basic and 0.90 (95% CI, 0.89-0.91) for the extended model. The proportion of false-negative results decreased from four of 248 (2%) to four of 317 (1%) with addition of CRP levels. False-positive results decreased from 113 of 195 (58%) to 87 of 178 (49%) after adding CRP levels. Limitations were potential risk of bias or applicability concerns in patient selection identified in the majority (five of eight) of the studies. In two of the studies, chest radiography was at the discretion of the physicians. The authors of the systematic review could not include all data from the eligible primary studies because the authors of three studies were not able to provide patient-level data. The prevalence of pneumonia in the primary studies varied widely and was generally higher than in

most primary care populations (two studies reporting 5%, three reporting 12% or 13%, two reporting 20%, and one reporting 43%). The authors of the systematic review concluded that adding CRP measurement to the diagnostic workup for suspected pneumonia in primary care improved the discrimination and risk classification of patients. It still left, however, a substantial group of patients classified as at intermediate risk, in which clinical decision-making remains challenging.

In addition to our review of evidence, we also examined the National Institute for Health and Care Excellence guideline for pneumonia in adults.[3] The guideline recommended that for people presenting with symptoms of lower respiratory tract infection in primary care, consider a point-of-care CRP test if, after clinical assessment, a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed. They recommended not routinely offering antibiotic therapy if the CRP level is < 20 mg/L.

Recommendations

1. For outpatient adults with acute cough due to suspected pneumonia, we suggest the following clinical symptoms and signs are suggestive of pneumonia (cough, dyspnea, pleural pain, sweating/fevers/shivers, aches and pains, temperature 38°C or greater, tachypnea and new and localizing chest examination signs) (Ungraded Consensus-Based Statement).

Remarks: The quality of evidence is low but the absence of runny nose and presence of breathlessness, crackles and/or diminished breath sounds on auscultation, tachycardia, and fever (38°C or greater) is suggestive of pneumonia.

2. For outpatient adults with acute cough due to suspected pneumonia, we suggest measuring C-reactive protein (CRP) because the addition of CRP to features such as fever (38°C or greater), pleural pain, dyspnea and tachypnoea, and signs on physical examination of the chest (tachypnea and new and localizing chest examination signs) strengthens both the diagnosis and exclusion of pneumonia (Grade 2C).

Remarks: The quality of evidence is low but a CRP >30 mg/L in addition to suggestive symptoms and signs increases the likelihood that the cough may be related to having pneumonia. Acute cough (ie, < 3 weeks in duration) is less likely to be caused by a pneumonia when the CRP <10 mg/L or between 10-50 mg/L in the absence of dyspnea and daily fever.

3. For outpatient adults with acute cough due to suspected pneumonia, we suggest not routinely measuring procalcitonin (Ungraded Consensus-Based Statement).

PICO Question 3

Should a diagnostic algorithm, clinical rule, or diagnostic score in addition to clinical judgment, compared with clinical judgment alone, be used to confirm the diagnosis of pneumonia in adult outpatients with acute cough?

Search Results: The search retrieved 27 publications. Abstract and title review of search results identified three studies for full-text review.[18-20] An additional four studies were identified from PICO question 1 retrieval as potentially eligible.[21-24] Because Metlay et al[20] is a systematic review including some of the primary studies, it was decided to exclude the meta-analysis and instead examine all of the primary studies retrieved. That left six primary studies meeting all inclusion criteria. After quality review using the modified QUADAS tool, only two were deemed to be of fair to good quality.[21,22] The reasons for study exclusion were primarily because they did not reflect an unbiased sample of patients for evaluation (eg, only patients already referred for chest radiographs were included). An evidence table of relevant data from the two studies was constructed.

Summary of Evidence and Discussion: Diehr et al[21] was a prospective cross-sectional study from 1984 that assessed the predictive value of signs and symptoms in patients with acute cough; 1,819 patients were included, and all had a complete history taken, physical examination performed, and chest radiographs obtained. The sample was divided into a derivation set and a validation set. Ultimately, a diagnostic rule was developed with seven signs and symptoms: rhinorrhea (−2 points), sore throat (−1 point), night sweats (+1 point), myalgia (+1 point), sputum all day (+1 point), respiratory rate > 25 breaths per minute (+2 points), and temperature > 100°F (+2 points). The score range was −3 to +6. According to the recommendation of the authors, if a score cutoff point of 0 was used to diagnose pneumonia with a sensitivity of 59% and specificity of 88%, then most patients with pneumonia would receive antibiotics and, compared with physician judgment alone, almost one-half the number of patients would receive antibiotics. Still, 41% of patients with pneumonia were missed at this cutoff point.

Emerman et al[22] was a prospective cross-sectional study that evaluated the decision rule developed by

Diehr et al[21] as well as the three other decision rules noted earlier. A total of 290 patients were included in the study, of whom 7% had pneumonia diagnosed based on chest radiographs. Overall, although physician judgment had the highest sensitivity for diagnosing pneumonia, the specificity of the different rules exceeded that of physician judgment, which potentially would result in significant reductions in use of chest radiographs and antibiotic treatment.

Three other articles have proposed decision rules for predicting pneumonia in patients with acute cough.[23-25] However, all three of these studies evaluated patients for whom physicians already had decided to order chest radiographs, introducing some bias into the estimates of sensitivity and specificity.

In a systematic review, Metlay et al[20] concluded that physician judgment alone frequently led to overestimation of the probability of pneumonia. Although individual signs and symptoms alone cannot rule in or rule out pneumonia, combinations of signs and symptoms can improve overall diagnostic accuracy. For example, the absence of any vital sign abnormalities has a high negative predictive value for ruling out pneumonia. However, even with the highest cutoff points for decision rules, the positive predictive value is rarely > 50%, reflecting the overall low frequency of pneumonia among all patients presenting with acute cough illness.

These studies assessed the diagnostic accuracy of clinical algorithms in comparison with chest radiography as the gold standard for pneumonia diagnosis. However, other studies have established that chest radiography is an imperfect gold standard because a significant proportion of pneumonia cases that initially are diagnosed based on higher-resolution imaging of the chest are not detected on chest radiographs.

Suggestion

4. For outpatient adults with acute cough and abnormal vital signs secondary to suspected pneumonia, we suggest ordering a chest radiography to improve diagnostic accuracy (Grade 2C).

PICO Question 4

Should microbiological testing in addition to clinical judgment, compared with clinical judgment alone, be used to confirm pneumonia in adult outpatients with acute cough?

Search Results: The search retrieved 199 publications. Abstract and title review identified seven articles for full-text review. No publications met all inclusion criteria.

Summary of Evidence and Discussion: Detection of a causative agent of CAP such that directed therapy is prescribed is considered a desirable goal. Although often regarded as a simple procedure, proper sputum collection has to account for adequacy of the sample to be free of oral contamination, transport time to the laboratory, preparation of a Gram stain, and incubation time. The values of the sputum culture results also depend on the pretest probability that the patient has bacterial pneumonia and on whether the patient has received prior antibiotics. In the likelihood a pathogen has been identified, the effect on antimicrobial management has been limited. Hence, the usefulness of pursuing routine sputum culture in patients with suspected CAP has been questioned on the basis of cost-effectiveness. Criteria for when a sputum culture would be indicated in cases of CAP have been published elsewhere.[5] As to the question of whether microbiological testing in addition to clinical judgment rather than clinical judgment alone be used to confirm pneumonia in outpatients with acute cough, the literature search identified no article addressing this question per se. Investigations of the microbiological testing for CAP included cough as one of the symptoms of CAP, but none of these studies reported outcomes solely based on cough with suspected pneumonia.

Suggestion

5. For outpatient adults with acute cough and suspected pneumonia, we suggest that there is no need for routine microbiological testing (Ungraded Consensus-Based Statement).

Remarks: Microbiologic testing should be considered if the results may result in a change of therapy.

PICO Question 5

Should antibiotics rather than no antibiotics be used to treat adult outpatients with acute cough and suspected pneumonia?

Search Results: The search retrieved 166 publications. Abstract and title review identified six articles for full-text review. No publications met all inclusion criteria.

Summary of Evidence and Discussion: This question addresses the situation of a patient with acute cough presenting with epidemiological and clinical findings suggesting a diagnosis of pneumonia but a confirmatory

chest radiograph not being available. We identified limited evidence specifically addressing this question. Recognizing that the sensitivity and specificity of both individual clinical symptoms and signs and clinical prediction rules based on the grouping of signs and symptoms to diagnose pneumonia are imperfect, and mindful of the need to maintain antibiotic stewardship, we extrapolate our recommendation from studies recommending the use of antibiotics in the treatment of patients with confirmed pneumonia.

Suggestions

6. For outpatient adults with acute cough, we suggest the use of empiric antibiotics as per local and national guidelines when pneumonia is suspected in settings where imaging cannot be obtained (Ungraded Consensus-Based Statement).

7. For outpatient adults with acute cough and no clinical or radiographic evidence of pneumonia (eg, when vital signs and lung exams are normal) we do not suggest the routine use of antibiotics (Ungraded Consensus-Based Statement).

In most settings, the radiographic evidence would be lack of consolidation on a chest radiograph.

PICO Question 6

Should nonantibiotic therapy rather than none be used to treat adult outpatients with acute cough and suspected pneumonia?

Search Results: The search retrieved 52 publications. Abstract and title review identified one guideline as meeting all inclusion criteria.[26] A review of the guideline for quality determined that the recommendation on nonantibiotic pharmacologic therapies was not developed from an evidence review, so the guideline was excluded from further consideration. An updated search of PubMed by using clinical queries at the end of 2016 identified a Cochrane review of supportive therapy that met eligibility criteria and was evaluated by means of the DART.[27] It met quality standards for good quality, and data were abstracted into an evidence table.

Summary of Evidence and Discussion: Interventions explored included cough suppressants, mucolytics, systemic corticosteroids, inhaled corticosteroids, anticholinergics, nonsteroidal antiinflammatory drugs, and vitamins C and D. The control group received antibiotics or placebo. The primary outcome evaluated was the proportion of participants who were not cured or not substantially improved at follow-up. Secondary outcomes

included the following: the proportion of patients with adverse events (eg, nausea, sleepiness, and so on), the proportion of patients with complications (eg, medication change regarding dose, duration, and so on), the proportion of patients requiring an outpatient care office visit, the proportion of patients requiring ED evaluation, and the proportion of patients requiring hospitalization.

From a systematic review,[27] there was only one RCT that compared the mucolytic bromhexine along with the antibiotic amoxicillin vs amoxicillin alone 4 times per day for 5 to 7 days. The main study included 392 adult patients but 101 in the subanalysis that related to acute pneumonia. These subjects were from 22 clinical centers throughout the Philippines. For the end point of cough not cured or not improved, the combined treatment did not improve this outcome (OR, 1.21; 0.48-3.04).[28]

Discussion: There is insufficient evidence to confirm or refute whether nonantibiotic, symptomatic therapy should be used routinely to treat outpatients with acute cough and suspected pneumonia. No recommendation can be made. RCTs are needed to explore this further.

PICO Question 7

Should antibiotics with atypical (cover with macrolides or fluoroquinolone) rather than antibiotics without atypical coverage be used to treat adult outpatients with acute cough and suspected pneumonia?

Search Results: The search retrieved 62 publications. No articles specifically addressed the role of antibiotic selection for the management of cough in outpatients with pneumonia. Seven studies and one systematic review addressing the broader question of antibiotic selection in the management of pneumonia were selected for full-text review. On full-text review of the studies, several were found to address inpatient rather than outpatient pneumonia, and one was not a systematic review. All were excluded from further analysis.

Summary of Evidence and Discussion: Our literature review disclosed no articles specifically addressing the role of antibiotic selection for the management of cough in outpatients with pneumonia. The Cochrane Central Register of Controlled Trials, MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature, Web of Science, and Latin American and Caribbean Health Sciences Literature databases were searched for RCTs published in peer-reviewed journals of antibiotics vs placebo as well as antibiotics vs other antibiotics for the treatment of CAP in outpatient

settings in patients older than 12 years. No studies of antibiotics vs placebo were found.

A systematic review was discovered and assessed as good by using DART methodology.[29] The Pakhale et al[29] review compared the efficacy and safety of different antibiotic treatments for CAP in participants older than 12 years treated in an outpatient setting with respect to clinical, radiologic, and bacteriologic outcomes. The review included 11 RCTs of good quality consisting of 3,352 participants older than 12 years with a diagnosis of CAP on the basis of clinical criteria and chest radiographs. Primary outcomes included test of clinical cure, improvement of signs and symptoms, and duration of clinical signs and symptoms. Secondary outcomes included radiologic response, bacteriologic response, adverse events, hospitalization, and mortality. Overall, there was no significant difference in the efficacy of various antibiotics in achieving the primary and secondary outcomes. The majority of studies assessed antibiotics with atypical coverage. Adverse effects, most of which were gastrointestinal, were reported in seven of the 11 studies.

PICO Question 8

Should antiviral therapy rather than no antiviral therapy be used to treat adults with acute cough and suspected or confirmed influenza? Does this reduce antibiotic prescriptions, general practice or primary care visits, ED visits, hospitalizations, or mortality?

Search Results: The search retrieved 276 publications. Abstract and title review identified 23 articles for full-text review. Eleven articles were evaluated further. Although cough was listed as one of the presenting symptoms with influenza, no publications addressing the use of antiviral agents in outpatients with acute cough and suspected influenza during the influenza season were identified.

Summary of Evidence and Discussion: The process identified two systematic reviews and meta-analyses[30,31] that examined the efficacy of oral and/or inhaled antiviral agents on patient-related outcomes for influenza or influenza-like illness. One systematic review was limited to RCTs,[30] and the other comprised only observational studies.[31] Among the antiviral agents evaluated were oseltamivir, laninamivir, zanamivir, and amantadine. Only a few studies adjusted for confounding variables, such as age and comorbid conditions, when reporting mortality or hospitalization. None of the meta-analyses addressed primary care or ED visits.

Jefferson et al[30] analyzed 23 studies of oseltamivir and 28 of zanamivir that were conducted during the

influenza season. Thirty-three were multicenter trials conducted in both hemispheres. Four were conducted in nursing homes. For oseltamivir treatment, there was no significant difference in hospitalization rate between treatment groups (risk ratio, 0.92; 95% CI, 0.57-1.50). Data on hospitalizations for the zanamivir studies were not reported. The oseltamivir trials did not detect any influenza-related deaths, reflecting the relatively benign nature of influenza in the study populations. The zanamivir trials detected eight deaths, of which only two were likely to be due to influenza, and both occurred in the intervention arms.

The systematic review and meta-analysis of observational studies by Hsu et al[31] consisted of 74 articles, the majority of which reported comparisons of oral oseltamivir with placebo or no antiviral therapy for treatment of laboratory-confirmed influenza or unconfirmed influenza-like illness. The analysis suggested that oseltamivir may reduce hospitalization in outpatients and decrease mortality in patients at high risk. Treatment was most effective when oral oseltamivir was started within 48 hours of symptom onset (OR, 0.33; 95% CI, 0.12-0.86 for mortality and OR, 0.52; 95% CI, 0.33-0.81 for hospitalization). When comparing inhaled zanamivir with no treatment, patients with laboratory-confirmed influenza or influenza-like illness were less likely to be hospitalized than were those who did not receive antiviral therapy. Studies that compared oral oseltamivir with inhaled zanamivir found no significant difference in hospitalization between the two groups. Overall, the quality of evidence was considered very low to low quality with respect to mortality and hospitalization. Only one study reported reduction in mortality in patients receiving oral amantadine; however, the quality of this body of evidence is very low because of serious risk of bias. Because of their well-known centrally active properties, adamantanes (amantadine and rimantadine) were considered more harmful than oseltamivir and zanamivir.

The association between antiviral therapy and antibiotic prescription was addressed in a case series involving older residents of long-term care facilities.[32] Compared with residents receiving no therapy or who became ill while taking antiviral therapy, residents who received oseltamivir within 48 hours of the onset of symptoms were less likely to be prescribed antibiotics (38% vs 20%; $P < .05$).

Suggestions

8. For outpatient adults with acute cough and suspected influenza, we suggest initiating antiviral

treatment (as per Centers for Disease Control and Prevention advice) within 48 hours of symptom onset. Antiviral treatment may be associated with decreased antibiotic usage, hospitalization, and improved outcomes (Ungraded Consensus-Based Statement).

Areas for Future Research

1. The implementation of the proposed suggestions should be audited in practice to assess feasibility and cost-effectiveness.
2. There is a need for improved diagnostic algorithms to confirm or refute whether acute cough is due to pneumonia or influenza.
3. To improve antimicrobial stewardship, RCTs are needed for pathogen-directed treatment of acute cough due to pneumonia vs standard therapy to determine whether personalizing antibiotic therapy will lead to clinical recovery and narrow the spectrum of antibiotic therapy used.
4. RCTs are needed to assess nonantibiotic, symptomatic therapies for acute cough due to pneumonia.

Conclusions

For outpatient adults with acute cough due to suspected pneumonia, there should be an assessment of clinical symptoms and signs, and those suspected of having pneumonia should undergo chest radiography to improve diagnostic accuracy. Although the measurement of CRP levels strengthens both the diagnosis and exclusion of pneumonia, there was no added benefit of measuring procalcitonin levels in this setting. Microbiological diagnostic testing should be considered when the results may indicate a change in therapy. For outpatient adults with acute cough, we suggest the use of empiric antibiotics when pneumonia is suspected based on epidemiologic and clinical features in settings in which imaging cannot be performed. Where there is no clinical or radiographic evidence of pneumonia, we do not suggest the routine use of antibiotics. There is insufficient evidence to make recommendations for or against specific nonantibiotic, symptomatic therapies. Finally, for outpatient adults with acute cough and suspected influenza, we suggest that initiating antiviral treatment within 48 hours of symptoms could be associated with decreased antibiotic use and hospitalization and improved outcomes.

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