Accuracy of Signs and Symptoms for the Diagnosis of Community-acquired Pneumonia: A Meta-analysis

Mark H. Ebell, MD, MS[1], Hulme Chupp, MPH[1]*, Xinyan Cai, MPH[1]*, Michelle Bentivegna, MPH[1]*, and Maggie Kearney, MPH[2]

ABSTRACT

Background: Community-acquired pneumonia (CAP) is an important source of morbidity and mortality. However, overtreatment of acute cough illness with antibiotics is an important problem, so improved diagnosis of CAP could help reduce inappropriate antibiotic use.

Methods: This was a meta-analysis of prospective cohort studies of patients with clinically suspected pneumonia or acute cough that used imaging as the reference standard. All studies were reviewed in parallel by two researchers and quality was assessed using the QUADAS-2 criteria. Summary measures of accuracy included sensitivity, specificity, likelihood ratios, the diagnostic odds ratio, and the area under the receiver operating characteristic curve (AUROCC) and were calculated using bivariate meta-analysis.

Results: We identified 17 studies, of which 12 were judged to be at low risk of bias and the remainder at moderate risk of bias. The prevalence of CAP was 10% in nine primary care studies and was 20% in seven emergency department studies. The probability of CAP is increased most by an abnormal overall clinical impression suggesting CAP (positive likelihood ratio [LR+] = 6.32, 95% CI = 3.58 to 10.5), egophony (LR+ = 6.17, 95% CI = 1.34 to 18.0), dullness to percussion (LR+ = 2.62, 95% CI = 1.14 to 5.30), and measured temperature (LR+ = 2.52, 95% CI = 2.02 to 3.20), while it is decreased most by the absence of abnormal vital signs (LR− = 0.25, 95% CI = 0.11 to 0.48). The overall clinical impression also had the highest AUROCC at 0.741.

Conclusions: While most individual signs and symptoms were unhelpful, selected signs and symptoms are of value for diagnosing CAP. Teaching and performing these high value elements of the physical examination should be prioritized, with the goal of better targeting chest radiographs and ultimately antibiotics.

Antibiotic overuse for patients with acute lower respiratory tract infection (LRTI) is widespread in the United States and around the world, in both primary care and emergency department (ED) settings.[1,2,3] It causes increasing rates of antibiotic resistance and increased costs and reinforces patient beliefs that every cough requires an antibiotic.[4] However, recently updated guidelines from the Infectious Diseases Society of America do recommend an antibiotic for patients with community-acquired pneumonia (CAP). Since it is not practical, safe, or cost-efficient to obtain a 0 (CXR) in all patients with a LRTI accompanied by cough, it is important to understand which elements of the history and physical examination can be used to identify patients at risk for CAP who may be candidates for a CXR and who does not need one.

From the [1]University of Georgia and [2]Department of Epidemiology, Athens, GA.
Received January 16, 2020; revision received March 4, 2020; accepted March 8, 2020.
*Order of authorship among three participating doctoral students and their contribution should be considered equal.
The authors have no relevant financial information or potential conflicts to disclose.
Author contributions: ME conceived and designed the study, participated in data abstraction, performed the primary analysis, and wrote the initial draft of the manuscript; CC, MB, XC, and MK all participated in abstraction of data for the meta-analysis; MB and CC duplicated the primary analysis by ME to confirm its accuracy; and all authors reviewed and approved the final manuscript.
Supervising Editor: Shahriar Zehtabchi, MD.
Address for correspondence and reprints: Mark H. Ebell, MD, MS; e-mail: ebell@uga.edu.
ACADEMIC EMERGENCY MEDICINE 2020;00:1–12.

doi: 10.1111/acem.13965
ISSN 1553-2712

In previous meta-analyses, we have shown that normal vital signs and a normal lung examination effectively rule out CAP in patients with acute cough,[5] that the overall clinical impression is moderately accurate for the diagnosis of CAP in adult,[6] and that C-reactive protein (CRP) is the preferred biomarker for the diagnosis of CAP in outpatients.[7] However, there has been no recent meta-analysis of the accuracy of individual signs and symptoms for the diagnosis of CAP in adults, with the most recent published in 2007.[8,9] In addition, previous meta-analyses did not use modern methods for the assessment of the quality of studies or to perform synthesis of measures of test accuracy.[10,11] We therefore set out to perform an updated meta-analysis using modern methods to answer the question: what is the accuracy of signs and symptoms for the diagnosis of CAP in adults.

METHODS

This was a meta-analysis of previously published studies of the accuracy of signs and symptoms for the diagnosis of CAP. The study was registered with the PROSPERO database (#CRD42018108036) and followed PRISMA guidance regarding conduct and reporting of a diagnostic meta-analysis (please see the Data Supplement S1, Appendix S1, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13965/full, for the PRISMA checklist).

Inclusion Criteria

Studies were included if they recruited a prospective cohort of adolescents or adults presenting with symptoms of respiratory infection or clinically suspected pneumonia (including when it was based on the physician ordering a CXR for respiratory symptoms) in the outpatient setting. The outpatient setting could include primary care, urgent care, and the ED. Studies had to report sufficient information to calculate sensitivity and specificity for the diagnosis of CAP for at least one sign or symptom (including vital signs). No limits were set for country, year, or language. The reference standard had to be imaging (radiography or CT) and had to have been performed in all participants or in all patients at high risk for pneumonia and a random sample of low-risk patients, to avoid verification bias.

Studies were excluded if they enrolled patients because they had dyspnea or sepsis rather than suspected CAP. They were also excluded if patients were in a specialized population such as only patients in skilled nursing facilities, immunosuppressed patients, or patients with chronic lung disease. Studies of ventilator or hospital-acquired pneumonia and studies of the diagnosis of a specific pathogen were excluded, although studies limited to older adults were included. Studies were excluded if they used a case–control design (i.e., recruited patients with known CAP and healthy controls or matched patients with and without radiographic pneumonia).

Search Strategy

This study is the second of three planned systematic reviews (biomarkers to diagnose CAP, signs and symptoms to diagnose CAP, and biomarkers for prognosis in CAP) that used a single search strategy. The search of the Medline database using the PubMed front-end was built around the concepts of "signs, symptoms, and biomarkers"; "community-acquired pneumonia"; and "accuracy or prognosis" linked by Boolean AND joins and is shown in Data Supplement S1, Appendix S2. The limits "has abstract," "human," and adult age ranges were applied to the search. In addition, the reference lists of included studies were reviewed for additional articles, as were two older systematic reviews identified by our search.[8,9]

Data Abstraction

All abstracts were reviewed for inclusion by the lead author (MHE) and by one of four graduate students in epidemiology (CC, MK, MB, or XC). For any abstract deemed potentially of interest, the full article was obtained and reviewed by the lead author and one other reviewer. Studies meeting inclusion and exclusion criteria were reviewed in parallel by the lead author and a graduate student who each abstracted variables describing study characteristics, study quality, and test accuracy data (true positives, true negatives, false negatives, and false positives). Discrepancies were resolved through consensus discussion.

Assessment of Study Quality

The QUADAS-2 tool was adapted for our study and definitions for low, unclear, and high risk of bias prespecified for each domain.[10] The full adapted tool is shown in Data Supplement S1, Appendix S3.

Analytic Strategy

Similar signs and symptoms were grouped together. For example, "purulent sputum," "sputum (purulent)," and "mucopurulent sputum" were grouped into a single variable called "sputum (purulent)." Both the original sign or the symptom name and new groupings are shown in the full data table in the Data Supplement S1, Appendix S3. For vital signs and other continuous variables, similar cutoffs to define an abnormal finding were combined where clinically reasonable, i.e., temperature greater than 37.7°C and temperature greater than 38.0°C. For studies reporting the overall clinical impression in multiple categories, "higher than 75%" and "quite sure" or "very sure" were defined as overall clinical impression of pneumonia.[12,13]

Data were imported into R (version 3.5.2) using the R Studio framework (version 1.1.463). We performed bivariate meta-analysis if there were three or more studies of a sign or symptom using the mada package (version 0.5.8) to calculate summary receiver operating characteristic (ROC) curves and measures of accuracy with 95% confidence intervals (CIs).[14] Where only a single study described the accuracy of a test and cutoff, we used the diagti procedure in Stata version 15.1 (StatCorp) to calculate measures of accuracy with 95% CIs.

Threshold effects occur when the cutoff for an abnormal test varies, resulting in a tradeoff between sensitivity and specificity. This can be an explicit variation in cutoff (e.g., in a biomarker such as CRP) or implicit for a sign or symptom (e.g., any cough vs. only moderate or severe cough). When a threshold effect was observed based on inspection of the summary ROC curve, we presented the ROC curve but did not necessarily report summary estimates of sensitivity and specificity. We reported the area under the ROC curves (AUROCCs) as a measure of overall discrimination where at least seven studies reported a sign or symptom and the likelihood ratio differed significantly from 1.0 (this threshold was determined post hoc after a review of the available studies). We also calculated summary estimates of diagnostic accuracy (sensitivity, specificity, likelihood ratios, and the diagnostic odds ratio) accompanied by 95% CIs. Positive and negative predictive values for typical prevalences of CAP in the outpatient setting are selectively reported for key signs and symptoms. Subgroup analyses were performed for selected signs and symptoms by inclusion criteria (patients were recruited because CXR was ordered vs. any patient with LRTI) and location (ED vs. primary care).

RESULTS

A total of 792 abstracts were identified by our search, as well as eight from the review of reference lists and one from the author's files. A bridge search was performed in August 2019 and identified 29 additional studies; one was reviewed in full but did not meet inclusion criteria. Thus, a total of 830 abstracts were reviewed, of which 141 were reviewed in full and 16 met our inclusion and exclusion criteria and were included in the final quantitative analysis. The search process is summarized in Figure 1.

Characteristics of included studies are summarized in Table 1. The setting for data collection was primary care for nine studies and the ED for seven studies, and the number of patients studied ranged from 52 to 2,820. The mean age of participants ranged from 32 to 62 years, and 48% to 60% were female. Nine studies were set in Europe, five in the United States, and one each in Israel and Chile. All studies used a new infiltrate or presence of radiographic diagnosis of pneumonia on chest x-ray as the reference standard test; we identified no studies that used CT as the reference standard. In one study, all patients where the clinician suspected pneumonia or with CRP> 50 mg/L received a CXR, as well as a 25% random sample of all other patients (n = 97); none of the latter were diagnosed with pneumonia.[15] Four studies only included patients where the physician felt a CXR was clinically indicated,[16,17,18,19] while the remainder included patients presenting with respiratory symptoms, whether or not the physician ordered a CXR. Because one study had somewhat different procedures for data collection in each of three states, in the assessment of study quality and the analysis each state was treated as a separate study.[18] In the nine primary care studies included in the current analysis, the prevalence of CAP was 10% (556/5,579), while it was 20% (584/2,928) in the seven ED studies.

Study quality was assessed using the QUADAS-2 framework and was judged to be low risk of bias for 12 studies and moderate risk of bias for five studies (Table 2). A detailed description of the assessment of study quality for each included study is shown in Data Supplement S1, Appendix S3.

The accuracy of studies is summarized in Table 3 (individual study level data are provided in Data Supplement S1, Appendix S6). The overall clinical impression was more helpful for ruling in than for ruling out CAP (positive likelihood ratio [LR+] = 6.32, 95%

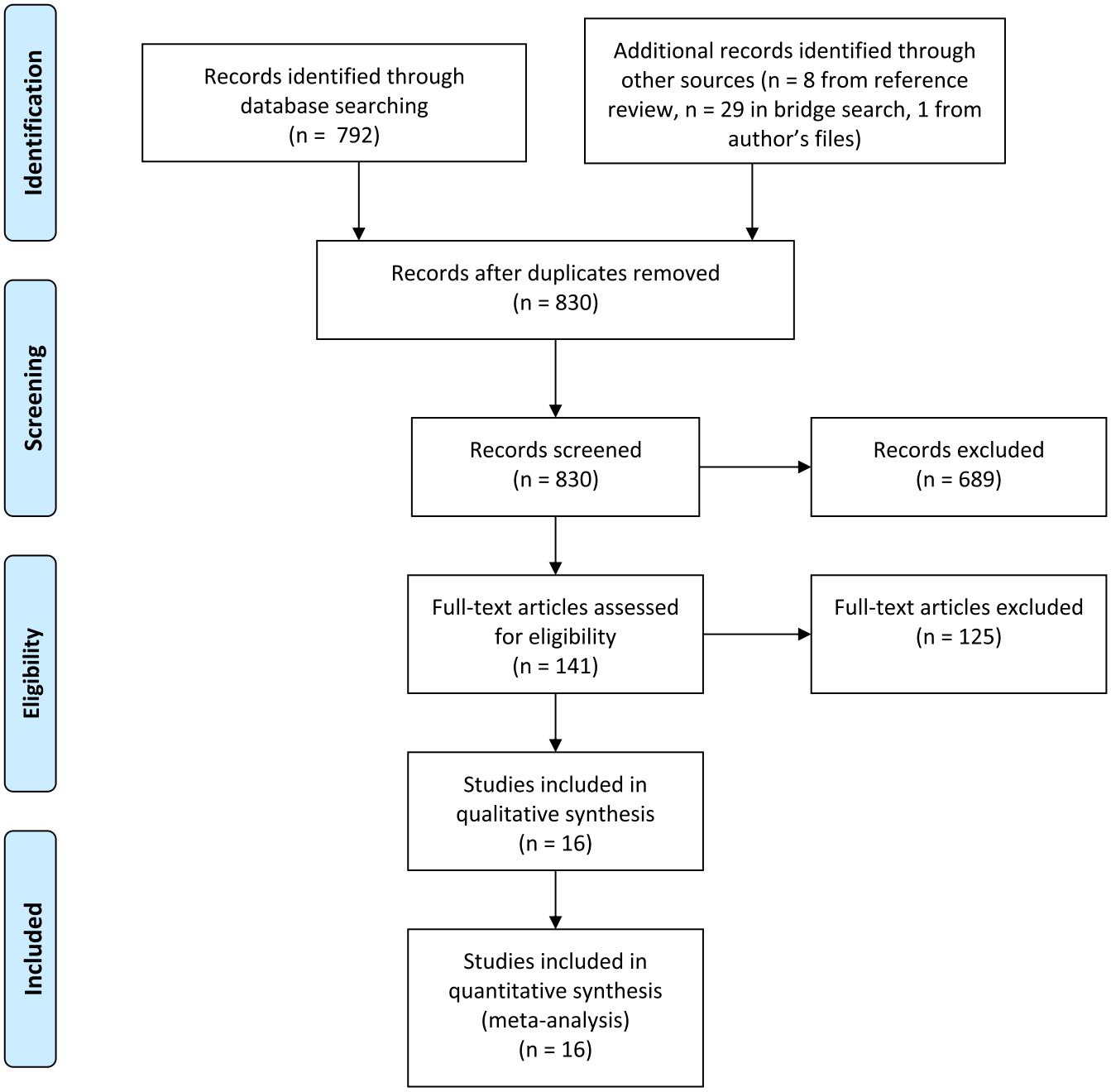

Figure 1. PRISMA flow diagram describing the search process

CI 3.58-10.5; negative likelihood ratio [LR−] = 0.54, 95% CI = 0.46 to 0.64). It had the highest LR + of any finding and also had the highest AUROCC at 0.741 (Figure 2) with no clear pattern regarding accuracy for patients enrolled in studies because they presented with acute RTI compared with those recruited because they had been referred for a CXR.

The only element of the medical history significantly associated with the likelihood of CAP based on the likelihood ratios was chronic obstructive pulmonary disease as a comorbidity (LR+ = 2.37, 95% CI = 1.21 to 4.33; LR− = 0.88, 95% CI = 0.78 to 0.97). Regarding patient-reported symptoms, subjective fever and chills, the absence of coryza and rhinorrhea, dyspnea, and chest pain significantly increased the likelihood of CAP when present (LR+ = 1.21 to 1.47) and reduce the likelihood of CAP when absent (LR− = 0.68 to 0.86). Cough had little discriminatory value, but this is likely because cough was usually required as an entrance criterion for the studies.

Egophony when present significantly increases the likelihood of CAP when present (LR+ = 6.17, 95% CI = 1.34 to 18.0), although the sensitivity is quite low and the CI broad. Other signs significantly

Table 1
Characteristics of Included Studies, Stratified by Setting (Primary Care or Other Outpatient Versus ED)

Author, Year	Number	Sex	Inclusion Criteria	Age	Reference Standard (Prevalence CAP)	Country	Years
Primary care							
Holm, 2007[28]	364	51% female	Consecutive adults 18 years or older with GP-diagnosed LRTI; excluded if recent hospitalization, severe illness requiring immediate hospitalization, pregnancy, or already in study	Median 50 years	CXR with new infiltrate (13.4%)	Denmark	2002–2003
Hopstaken, 2003[29]	246	NR	Consecutive adults 18 years or older with acute LRTI defined as new or worsening cough and other clinical characteristics; excluded if pregnant/lactating, antibiotic allergy, other severe disease, or recent hospitalization or antibiotics.	Mean 52 years	CXR with new infiltrate (13.2%)	Netherlands	1998–1999
Lieberman, 2003[30]	250	53% female	Febrile adult 21 years or older with at least one of cough, coryza, sore throat, or hoarseness	Mean 40 years	CXR with new infiltrate that resolved after treatment (7.6%)	Israel	1999
Melbye, 1988[12]	71	48% female	Patients age 15 years or older with LRTI suspected to be CAP	Mean 48 years	CXR with new infiltrate that resolved at 4 weeks (15.5%)	Norway	1986
Melbye, 1992[15]	581	58% female	Patients age 18 years or older presenting with symptoms suggestive of respiratory or throat infection	Mean 32 years	CXR showing a density that resolved on follow-up (5.0%)	Norway	1988–1989
Moberg, 2016[13]	100	55% female	Physician-suspected CAP, age 18+ years, and respiratory symptoms for at least 24 hours	Mean 56 years	CXR with new infiltrate (45.0%)	Sweden	2011–2014
Moore, 2017[16]	720	49% female	Acute cough as the main symptom, judged to be infective by treating physician, 16+ years, and had CXR ordered by treating physician due to suspicion of pneumonia	45% were 60 years or older	CXR with possible, probable, or definite pneumonia (16.0%)	United Kingdom	2009–2013
van Vugt, 2013[22]	2820	60% female	Patients 18 years and older with acute cough or clinically suspected as having LRTI	Mean 50 years	CXR with new infiltrate (5.0%)	12 European countries	2007–2010
Steurer, 2011[31]	464	50% female	Patients age 18 years or older with cough and subjective or objectively measured fever. Excluded if known chronic lung disease other than chronic bronchitis or immunosuppression.	Mean 47 years	CXR with radiographic shadowing for which there is no other explanation (20.5%)	Switzerland	2006–2009
ED							
Wipf, 1999[32]	52	0% female	Adults with new or worsening cough accompanied by increased or darkening sputum production	Mean 62 years	CXR with new infiltrate (46.2%)	United States	1990–1993
Diehr, 1984[33]	483	51% female	Adults with cough less than 1 month duration; excluded if pregnant	Mean 40 years	CXR with radiographic pneumonia (9.9%)	United States	NR
Gennis, 1989[19]	308	43% female	Patients 16 years or older where a CXR had been ordered to evaluate for possible CAP; excluded if pregnant	Mean 54 years	CXR interpreted as positive or equivocal for pneumonia (38.3%)	United States	1984–1985
Gonzalez Ortiz, 1995[34]	141	NR	Patients 15 years or older presenting with fever (>38°C) and respiratory symptoms; excluded if focal signs suggesting other infection such as meningitis	NR	CXR with findings suggestive of pneumonia (37.6%)	Spain	NR

(Continued)

Table 1 (continued)

Author, Year	Number	Sex	Inclusion Criteria	Age	Reference Standard (Prevalence CAP)	Country	Years
Saldías, 2007[35]	325	59% female	Patients 15 years or older with fever or respiratory symptoms presenting to the ED. Excluded if immunocompromised or chronic lung disease.	Mean 53 years	CXR with radiographic pneumonia (34.5%)	Chile	2005
Singal, 1989[17]	255	58% female	Patients 18 years or older where a CXR had been ordered to evaluate for possible CAP	Mean 54 years	CXR interpreted as positive, equivocal, or possible infiltrate (15.7%)	United States	1986–1987
Tape, 1991[18]	1364	58% female	Physician thought pneumonia was a possibility or at least two of fever, cough, sputum, pleuritic pain, dyspnea, wheeze, or altered mentation and CXR had been ordered	Mean 45.4 years Illinois, 47.6 years Nebraska, and 41 years Virginia	CXR interpreted as probable or definite pneumonia (13.9%)	United States	1987–1988

CAP = community-acquired pneumonia; CXR = chest radiograph; GP = general practitioner; NR = not reported.

associated with an increased risk of CAP include dullness to percussion, confusion, crackles, decreased breath sounds, any abnormal lung founds, the presence of rhonchi, and toxic or ill-appearance (LR+ = 1.46 to 2.62). As with symptoms, the absence of a finding had less effect on reducing the likelihood of CAP (LR− = 0.61 to 0.96) than its presence did on increasing it.

Abnormal vital signs were also associated with an increased risk of CAP, including measured temperature ≥ 37.7 to 38.0°C, O_2 saturation < 95%, heart rate> 100 beats/min, and respiratory rate> 20 to 25/min (LR+ = 2.02 to 2.52). The absence of any abnormal vital signs had a negative likelihood ratio of 0.25, providing good evidence against the presence of CAP.

Only the presence of "any abnormal vital sign" had a sensitivity above 80% (93%), while clinical characteristics with a specificity greater than 90% were history of chronic obstructive pulmonary disease, egophony, dullness to percussion, and confusion. Clinical characteristics with a positive likelihood ratio greater than 2.5 include egophony, dullness to percussion, confusion, and measured temperature greater than 37.7 to 38.0°C. Only the absence of any abnormal vital sign had a negative likelihood ratio less than 0.5, at 0.25. The highest AUROCCs were found for the overall clinical impression (0.741), any abnormal lung finding (0.669), and measured temperature greater than 37.7 to 38.0°C (0.637).

Another measure of overall diagnostic accuracy or discrimination is the diagnostic odds ratio (DOR). Findings with the highest DOR for the diagnosis of CAP were the overall clinical impression (11.5, 95% CI = 6.7-18.5), egophony (6.5, 95% CI = 1.4-18.9), and any abnormal vital sign (6.0, 95% CI = 3.0-10.6).

Comparing studies of patients recruited because they had a CXR ordered versus studies that recruited all patients with acute RTI, there was no clear pattern for the accuracy of abnormal lung examination, chest pain, crackles, dullness to percussion, dyspnea, or tachycardia when stratified by these variables (Data Supplement S1, Appendix S4). We also compared studies set in the ED with those set in primary care for selected signs and symptoms where there were an adequate number of studies in each setting. There was no clear pattern for overall clinical impression or crackles on examination. For the symptom of dyspnea, all five studies in the primary care setting were more sensitive than the ED studies, while all four ED

Table 2
Overview of Study Quality

	Patient Selection	Index Test	Reference Standard	Flow and Timing	L = 0, M = 1, and H = 2 + With High Likelihood of Bias
Diehr, 1984[33]	L	L	L	L	L
Gonzalez Ortiz, 1995[34]	L	L	L	L	L
Holm, 2007[28]	L	L	L	L	L
Hopstaken, 2003[29]	L	L	L	L	L
Lieberman, 2003[30]	L	L	L	L	L
Melbye, 1988[12]	L	L	L	L	L
Moore, 2017[16]	L	L	L	L	L
Saldías, 2007[35]	L	L	L	L	L
Steurer, 2011[31]	L	L	L	L	L
van Vugt, 2013[22]	L	L	L	L	L
Wipf, 1999[32]	L	L	L	L	L
Tape (Nebraska, Illinois), 1991[18]*	L	L	L	L	L
Singal, 1989[17]	H	L	L	L	M
Moberg, 2016[13]	L	L	H	L	M
Melbye, 1992[15]	L	L	L	H	M
Gennis, 1989[19]	H	L	L	L	M
Tape (Virginia), 1991[18]*	L	L	H	L	M

*Because this study used different data collection procedures in Virginia, quality is assessed separately for that state.

studies were more specific than the primary care studies (Data Supplement S1, Appendix S5).

DISCUSSION

The history and physical examination is a critical component of the evaluation of patients with acute cough. However, many individual signs and symptoms have limited value (especially when absent), and knowledge of the signs and symptoms most predictive of CAP can help physicians focus their evaluation. Based on the DOR, a measure of overall discrimination, the following elements of the clinical examination are most useful: the overall clinical impression, the presence of egophony, any abnormal vital sign, any abnormal lung finding, tachypnea, and the presence of measured fever. Based on the comparison of subjective with objective temperature, one concludes that the absence of subjective fever helps rule out CAP, while the presence of measured fever tends to rule it in (Figure 2). However, the converse (absence of measured fever or presence of subjective fever) is less helpful diagnostically.

The LR + and LR– for a number of signs and symptoms that are often acquired as part of the history and physical examination such as dullness to percussion, confusion, crackles, decreased breath sounds, any abnormal lung founds, the presence of rhonchi, and toxic or ill appearance were significantly associated with the presence or absence of CAP. However, the likelihood ratios were all between 0.5 and 2.0 for these findings, so they have little impact on the diagnostic likelihood of CAP and were especially unhelpful when negative. On the other hand, physician integration of individual signs and symptoms has much higher diagnostic accuracy. This has been previously shown—that the overall clinical impression can approximate the accuracy of a clinical prediction rule.[20]

The summary ROC curve for overall clinical impression shows data consistent with a threshold effect for studies including any patient with acute RTI. For those who were only included if a CXR was ordered, specificity was consistent but sensitivity varied, perhaps due to differences in the threshold for ordering the test. Review of the summary ROC curve for fever (Figure 3) revealed that subjective fever was more sensitive (63% vs. 34%) but less specific (55% vs. 87%) than measured temperature> 37.7 to 38.0°C for the diagnosis of CAP.

The symptom of dyspnea showed a pattern of diagnostic accuracy by setting, being more sensitive in primary care and more specific in the ED. This may reflect different implicit cutoffs, with primary care

Table 3
Diagnostic accuracy for individual elements of the medical history and physical examination

Sign or symptom	Studies (patients)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR− (95% CI)	Diagnostic odds ratio (95% CI)	AUROCC
Overall clinical impression	7 (5081)	0.50 (0.39-0.61)	0.92 (0.84-0.96)	**6.32 (3.58-10.5)**	**0.54 (0.46-0.64)**	**11.5 (6.7-18.5)**	0.741
Medical history							
Chronic obstructive pulmonary disease	3 (748)	0.19 (0.13-0.27)	0.91 (0.86-0.95)	**2.37 (1.21-4.33)**	**0.88 (0.78-0.97)**	**2.74 (1.24-5.51)**	
Previous pneumonia	3 (1245)	0.13 (0.02-0.47)	0.90 (0.63-0.98)	1.32 (0.81-2.00)	0.96 (0.81-1.02)	1.39 (0.79-2.21)	
Any comorbidity	3 (3904)	0.44 (0.33-0.55)	0.63 (0.50-0.75)	1.19 (0.99-1.48)	0.90 (0.80-1.01)	1.34 (0.98-1.80)	
Alcohol use disorder	3 (988)	0.06 (0.02-0.23)	0.96 (0.93-0.98)	NC	NC	NC	
Smoking (current)	4 (3425)	0.32 (0.13-0.59)	0.69 (0.54-0.81)	1.06 (0.53-1.78)	0.97 (0.66-1.22)	1.18 (0.44-2.73)	
Male sex	4 (3539)	0.46 (0.39-0.54)	0.57 (0.52-0.61)	1.08 (0.93-1.23)	0.94 (0.83-1.06)	1.15 (0.88-1.47)	
Smoking (ever)	3 (1434)	0.50 (0.30-0.69)	0.52 (0.36-0.67)	1.03 (0.78-1.28)	0.97 (0.75-1.18)	1.09 (0.66-1.70)	
Symptoms							
Pleuritic chest pain	3 (1245)	0.32 (0.26-0.39)	0.87 (0.65-0.96)	2.76 (0.97-7.133)	0.81 (0.70-1.02)	3.56 (0.95-9.77)	
Fever (subjective)	8 (4907)	0.63 (0.50-0.74)	0.55 (0.38-0.71)	**1.47 (1.26-1.71)**	**0.68 (0.58-0.80)**	**2.10 (1.48-2.87)**	0.623
Chills	7 (2453)	0.55 (0.43-0.67)	0.62 (0.50-0.72)	**1.44 (1.26-1.65)**	**0.73 (0.63-0.83)**	**2.00 (1.58-2.49)**	0.610
Coryza and rhinorrhea absent	4 (1106)	0.60 (0.40-0.77)	0.57 (0.22-0.66)	**1.43 (1.11-2.00)**	**0.71 (0.56-0.86)**	**2.07 (1.31-3.13)**	
Sputum (bloody)	4 (1582)	0.13 (0.06-0.27)	0.90 (0.84-0.94)	1.33 (0.80-2.06)	0.96 (0.84-1.02)	1.41 (0.78-2.47)	
Dyspnea	10 (5626)	0.63 (0.48-0.75)	0.51 (0.31-0.71)	**1.30 (1.07-1.65)**	**0.75 (0.66-0.85)**	**1.75 (1.28-2.34)**	0.598
Sore throat absent	3 (782)	0.60 (0.49-0.70)	0.52 (0.28-0.75)	1.29 (0.75-1.77)	0.81 (0.57-1.34)	1.78 (0.65-3.83)	
Chest pain	8 (5031)	0.51 (0.33-0.69)	0.58 (0.37-0.76)	**1.21 (1.05-1.42)**	**0.86 (0.78-0.94)**	**1.41 (1.13-1.74)**	0.549
Headache	3 (1188)	0.65 (0.46-0.81)	0.42 (0.21-0.65)	1.19 (0.93-1.49)	0.85 (0.67-1.08)	1.35 (0.90-1.94)	
Sputum (any)	6 (4441)	0.71 (0.60-0.81)	0.35 (0.21-0.51)	1.11 (0.96-1.32)	0.84 (0.63-1.11)	1.37 (0.87-2.07)	
Myalgias	3 (1424)	0.49 (0.41-0.56)	0.57 (0.45-0.68)	1.10 (0.91-1.45)	0.92 (0.77-1.10)	1.26 (0.82-1.86)	
Sputum (purulent)	3 (1365)	0.52 (0.35-0.70)	0.52 (0.39-0.65)	1.09 (0.90-1.26)	0.92 (0.73-1.08)	1.21 (0.83-1.71)	
Cough	7 (1866)	0.88 (0.82-0.93)	0.16 (0.07-0.34)	1.07 (0.97-1.27)	0.77 (0.41-1.37)	1.57 (0.71-3.01)	
Signs							
Egophony	3 (1116)	0.05 (0.03-0.10)	0.99 (0.95-0.99)	**6.17 (1.34-18.0)**	**0.96 (0.93-0.99)**	**6.46 (1.36-18.9)**	
Dullness to percussion	7 (1932)	0.14 (0.10-0.19)	0.94 (0.88-0.97)	**2.62 (1.14-5.30)**	**0.92 (0.87-0.98)**	**2.89 (1.17-5.90)**	NC
Confusion	4 (1596)	0.11 (0.08-0.15)	0.95 (0.92-0.97)	**2.15 (1.36-3.34)**	**0.94 (0.90-0.98)**	**2.29 (1.39-3.63)**	
Crackles	12 (5898)	0.42 (0.32-0.52)	0.79 (0.68-0.86)	**2.00 (1.54-2.58)**	**0.74 (0.66-0.82**	**2.70 (1.95-3.63)**	0.611
Decreased breath sounds	6 (4322)	0.25 (0.20-0.32)	0.87 (0.78-0.92)	**1.96 (1.23-3.02)**	**0.87 (0.79-0.95)**	**2.29 (1.31-3.73)**	
Abnormal lung exam (any finding)	8 (2875)	0.60 (0.40-0.78)	0.67 (0.42-0.85)	**1.90 (1.26-2.91)**	**0.61 (0.47-0.75)**	**3.18 (1.83-2.08)**	0.669
Rhonchi	5 (2375)	0.23 (0.16-0.32)	0.87 (0.78-0.92)	**1.76 (1.26-2.41)**	**0.89 (0.83-0.95)**	**1.99 (1.35-2.81)**	
Toxic or ill appearance	5 (4162)	0.42 (0.22-0.65)	0.70 (0.43-0.88)	**1.46 (1.08-2.15)**	**0.83 (0.71-0.94)**	**1.77 (1.17-2.64)**	
Pleural rub	5 (1885)	0.07 (0.04-0.11)	0.97 (0.91-0.992)	3.02 (0.74-8.02)	0.96 (0.91-1.02)	3.20 (0.72-8.81)	
Wheeze (any)	8 (2519)	0.25 (0.19-0.32)	0.75 (0.68-0.92)	1.00 (0.82-1.22)	1.00 (0.94-1.07)	1.00 (0.77-1.30)	
Vital signs							
Temp>=37.7-38.0	10 (5490)	0.34 (0.25-0.56)	0.87 (0.79-0.92)	**2.52 (2.02-3.20)**	**0.77 (0.70-0.83)**	**3.30 (2.60-4.16)**	0.637
O2 saturation < 95%	3 (1089)	0.36 (0.22-0.53)	0.83 (0.78-0.87)	**2.12 (1.47-2.71)**	**0.77 (0.61-0.92)**	**2.83 (1.61-4.39)**	
Heart rate> 100 bpm	8 (5172)	0.33 (0.23-0.44)	0.84 (0.74-0.90)	**2.04 (1.59-2.62)**	**0.80 (0.73-0.86)**	**2.55 (1.93-3.31)**	0.606
Respiratory rate> 20-25 bpm	3 (3638)	0.53 (0.25-0.79)	0.84 (0.44-0.91)	**2.02 (1.34-3.02)**	**0.65 (0.45-0.84)**	**3.14 (2.08-4.51)**	
Any abnormal vital sign	3 (604)	0.93 (0.74-0.98)	0.30 (0.12-0.59)	**1.37 (1.10-1.84)**	**0.25 (0.11-0.48)**	**6.01 (3.03-10.6)**	

Where the positive likelihood ratio (LR+), negative likelihood ratio (LR−) or diagnostic odds ratio differed significantly from 1.0, the value is shown in bold face.
NC, not calculable from data; AUROCC = area under the receiver operating characteristic curve.

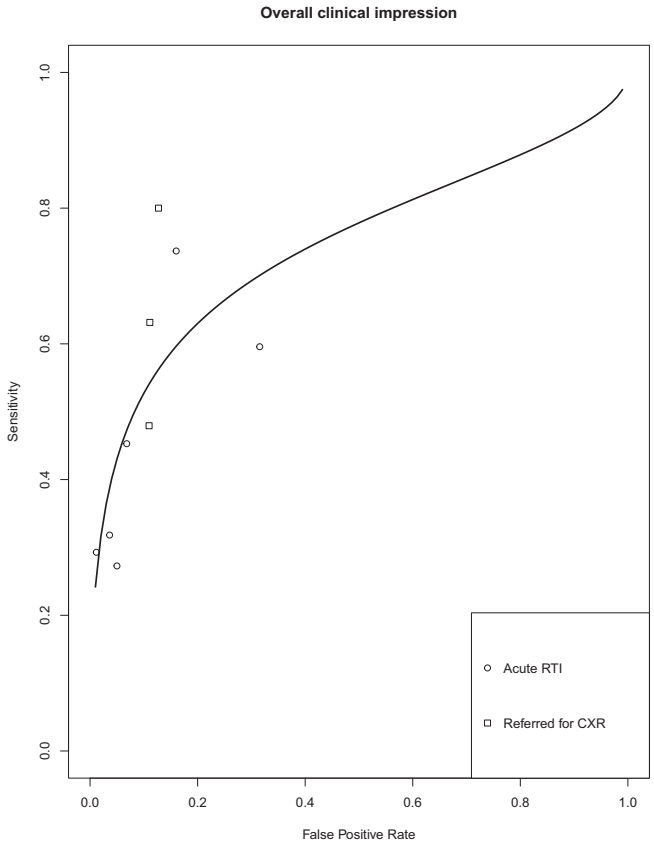

Figure 2. Summary receiver operating characteristic curve for the overall clinical impression. CXR = chest radiograph; RTI = respiratory tract infection

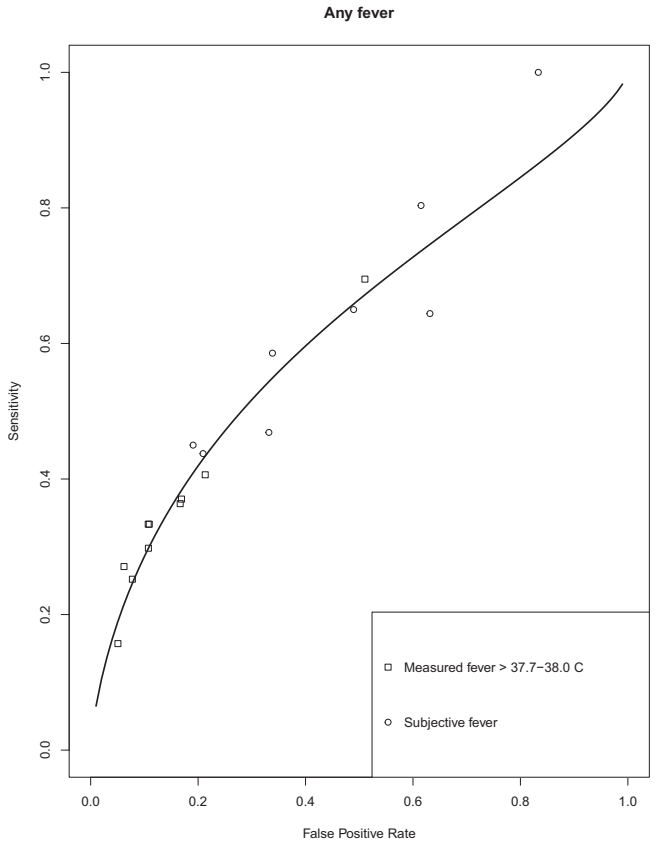

Figure 3. Summary receiver operating characteristic curve for subjective fever versus measured temperature> 37.7 to 38.0°C

physicians using a lower threshold for diagnosing CAP to achieve a higher sensitivity, so appropriate patients can be referred to the ED for further evaluation.

While guidelines recommend a CXR to confirm the diagnosis of CAP before initiating therapy,[21] not all patients with acute cough should receive a CXR. Also, CXRs may not be readily available outside of the ED setting or in low resource settings. The presence of an overall clinical impression suggesting CAP (LR+ = 6.3, 95% CI = 3.6 to 10.5), egophony (LR+ = 6.2, 95% CI = 1.3 to 18.0), dullness to percussion (LR+ = 2.6, 95% CI = 1.1 to 5.3), and measured fever (LR+ = 2.5, 95% CI = 2.0 to 3.2) were all moderately useful for increasing the likelihood of CAP and could prompt a clinician to order a radiograph in a patient with acute cough. Only a single clinical finding had a LR– less than 0.5 (absence of any abnormal vital sign), while the past medical history and comorbidities were of relatively little diagnostic value.

Combinations of symptoms were not generally studied, other than any abnormal lung finding (LR+ = 1.9, 95% CI = 1.3 to 2.9; LR– = 0.61, 95% CI = 0.47 to 0.75) and any abnormal vital sign (LR+ = 1.4, 95% CI = 1.1 to 1.8; LR– = 0.25, 95% CI = 0.11 to 0.48). Thus, normal vital signs provide reassurance that CAP is less likely, and we showed in a previous systematic review that the combination of normal vital signs and normal lung examination has a negative likelihood ratio of 0.1 for CAP.[5] The combination of normal vital signs and a normal lung examination would reduce the likelihood of CAP to approximately 0.5% given a prevalence of 5%, 1% given a prevalence of 10%, and 2% given a prevalence of 20%, obviating the need for a chest x-ray in most patients. On the other hand, an abnormal overall clinical impression or the presence of egophony would increase the likelihood of CAP to 25% given a prevalence of 5%, 36% given a prevalence of 10%, and 56% given a probability of 20%, situations in which a chest x-ray (and possibly empiric therapy) would be appropriate for most patients. The excellent test characteristics of the overall clinical impression mean that experienced ED and primary care physicians can trust their overall judgment of the likelihood of pneumonia and value it is a diagnostic test. It is also an important message for physicians that we should not rely too much on the

absence of individual physical findings such as egophony, dullness to percussion, crackles, decreased breath sounds, or rhonchi, which all have summary estimates of the LR– between 0.74 and 0.96.

Knowing how to best use signs and symptoms can help physicians avoid inappropriate antibiotic use. Those with normal vitals and a normal lung examination (in the absence of other bacterial infections such as streptococcal pharyngitis or acute otitis media, which are easily ruled out) should not receive antibiotics. Knowing that the likelihood of CAP is extremely low can bolster the confidence of physicians not to prescribe an antibiotic. For those at increased risk of CAP based on the overall clinical impression or the presence of one or more signs, a negative CXR can again provide confidence not to prescribe antibiotics. By targeting CXR, we also avoid its overuse.

An open question is the degree of statistical independence of individual signs, symptom, vital signs, and the CRP. In a previous study by van Vugt and colleagues,[22] the presence of crackles, diminished vesicular breathing, tachycardia, fever, the absence of rhinorrhea, and elevated CRP were all independent predictors of CAP, suggesting that CRP provides diagnostic value in addition to that of the physical examination.

Van Vugt et al.[22] also identified several clinical prediction rules for the diagnosis of CAP, but none performed particularly well as measured by the AUROCC either in the study population in van Vugt et al. or in a small validation study by Graffelman et al.[23] Van Vugt and colleagues[22] have proposed their own clinical prediction rule based on the largest study to date, but it has yet to be prospectively validated. It would also be worth exploring novel modeling strategies such as artificial neural networks or fast and frugal trees, as well as a two-stage process for clinical diagnosis. For example, those with normal vital signs and normal examination can be excluded at stage 1, in stage 2 a clinical prediction rule used to identify those at high risk for CAP who should all undergo CXR, and in a moderate-risk group where clinicians would use their judgement and other sources of information.

In the past 2 years, our group has now performed a set of four related systematic reviews on the diagnosis of CAP. We conclude that the overall clinical impression is a valuable diagnostic tool, with accuracy similar to that of clinical prediction rules.[6] Most of the studies in that review included experienced clinicians rather than trainees. How to best teach this skill of "clinical gestalt," how many exposures to patients with acute respiratory illness are needed to develop it, and how to best integrate it with other information remain to be determined. The same questions apply to egophony, which had the highest LR + but which not all physicians may be comfortable eliciting. We also concluded that patients with normal lung findings and normal vital signs are very unlikely to have CAP (LR– = 0.1).[5] Finally, CRP is moderately accurate for the diagnosis of CAP (AUROCC = 0.82; M.H. Ebell, submitted for publication) and has also been shown to be a tool that can reduce inappropriate antibiotic use.[24–26]

STRENGTHS AND LIMITATIONS

Strengths of the current study include a comprehensive literature search, the generally good methodologic quality of included studies, and the use of contemporary bivariate meta-analysis. Limitations include heterogeneity in clinical settings and countries, differences in the inclusion criteria, and a failure to define what is abnormal for a sign or symptom. In addition, some signs and symptoms such as the overall clinical impression had likelihood ratios with relatively wide CIs (LR+ = 6.3, 95% CI = 3.6 to 10.5). While there was a fairly broad range of prevalence of CAP in the included studies, this should not impact sensitivity, specificity, or LRs, which are characteristics of the test. Finally, all studies used chest radiography as the reference standard, which is imperfect. In one study of 2,251 patients who received both CXR and CT, 97% of patients had pneumonia diagnosed on both studies, and only 3% had pneumonia only seen on CT.[27]

CONCLUSION

In conclusion, while the history and physical examination is important, only a few key signs and symptoms significantly change the underlying likelihood of community-acquired pneumonia. The probability of community-acquired pneumonia is appreciably increased by an overall clinical impression suggesting community-acquired pneumonia, egophony, dullness to percussion, and measured temperature, while it is significantly decreased by the absence of abnormal vital signs or (from a previous study) the combination of abnormal vital signs and a normal lung examination.[5] Clinical education should focus on teaching

high-value elements of the examination such as egophony or dullness on percussion and on providing sufficient clinical examples of acute cough to hone the overall clinical impression. Future research should be performed to validate promising clinical prediction rules and to integrate signs, symptoms, and point-of-care tests such as C-reactive protein and to explore novel approaches to the development and validation of these rules.

References

1. Antimicrobial Resistance Posing Growing Health Threat. Available at: http://www.cdc.gov/media/releases/2011/p0407_antimicrobialresistance.html. Accessed Mar 30, 2020.
2. Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011. JAMA 2016;315:1864–73.
3. Joint Commission. Antimicrobial Stewardship Tools. 2015. Available at: http://www.jointcommission.org/topics/hai_portal_external_resources_antimicrobial_stewardship.aspx. Accessed Mar 30, 2020.
4. Little P, Rumsby K, Kelly J, et al. Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomized controlled trial. J Am Med Assoc 2005;293:3029–35.
5. Marchello CS, Ebell MH, Dale AP, Harvill ET, Shen Y, Whalen CC. Signs and symptoms that rule out community-acquired pneumonia in outpatient adults: a systematic review and meta-analysis. J Am Board Fam Med 2019;32:234–47.
6. Dale AP, Marchello C, Ebell MH. The accuracy of the overall clinical impression for the diagnosis of pharyngitis, sinusitis, and pneumonia: a meta-analysis. Br J Gen Pract 2019;69:e444–53.
7. Ebell MH, Bentivegna M, Cai X, Hulme C, Kearney M. Accuracy of biomarkers for the diagnosis of adult communityacquired pneumonia: a meta-analysis. Acad Emerg Med 2020; 27:195–206.
8. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. JAMA 1997;278:1440–5.
9. Müller B, Harbarth S, Stolz D, et al. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. BMC Infect Dis 2007;7:10.
10. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.
11. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol 2005;58:982–90.
12. Melbye H, Straume B, Aasebo U, Brox J. The diagnosis of adult pneumonia in general practice. The diagnostic value of history, physical examination and some blood tests. Scand J Prim Heal Care 1988;6:111–7.
13. Moberg AB, Taleus U, Garvin P, Fransson SG, Falk M. Community-acquired pneumonia in primary care: clinical assessment and the usability of chest radiography. Scand J Prim Heal Care 2016;34:21–7.
14. Doebler P. mada: Meta-Analysis of Diagnostic Accuracy. R package version 0.5.8. 2017. Available at: https://cran.r-project.org/package=mada. Accessed Mar 30, 2020.
15. Melbye H, Straume B, Aasebøs U, Dale K. Diagnosis of pneumonia in adults in general practice relative importance of typical symptoms and abnormal chest signs evaluated against a radiographic reference standard. Scand J Prim Health Care 1992;10:226–33.
16. Moore M, Stuart B, Little P, et al. Predictors of pneumonia in lower respiratory tract infections: 3C prospective cough complication cohort study. Eur Respir J 2017;50: pii:1700434.
17. Singal BM, Hedges JR, Radack KL. Decision rules and clinical prediction of pneumonia: evaluation of low-yield criteria. Ann Emerg Med 1989;18:13–20.
18. Tape TG, Heckerling PS, Ornato JP, Wigton RS. Use of clinical judgment analysis to explain regional variations in physicians' accuracies in diagnosing pneumonia. Med Decis Mak 1991;11:189–97.
19. Gennis P, Gallagher J, Falvo C, Baker S, Than W. Clinical criteria for the detection of pneumonia in adults: guidelines for ordering chest roentgenograms in the emergency department. J Emerg Med 1989;7:263–8.
20. Dale AP, Marchello C, Ebell MH. Clinical gestalt to diagnose pneumonia, sinusitis, and pharyngitis: a meta-analysis. Br J Gen Pract 2019;69:e444–53.
21. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and infectious diseases Society of America. Am J Respir Crit Care Med. 2019;200:e45–67.
22. van Vugt SF, Broekhuizen BD, Lammens C, et al. Use of serum C reactive protein and procalcitonin concentrations in addition to symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough: diagnostic study. BMJ 2013; 346:f2450.
23. Graffelman AW, Le Cessie S, Knuistingh Neven A, Willemssen FE, Zonderland HM, Van Den Broek PJ. Can history and exam alone reliably predict pneumonia? J Fam Pract 2007;56:465–70.

24. Aabenhus R, Jensen JU, Jorgensen KJ, Hrobjartsson A, Bjerrum L. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. Cochrane Database Syst Rev 2014;(6):CD010130.
25. Cals JW, Ebell MH. C-reactive protein: guiding antibiotic prescribing decisions at the point of care. Br J Gen Pract 2018;68:112–3.
26. Cals JW, Schot MJ, de Jong SA, Dinant GJ, Hopstaken RM. Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. Ann Fam Med 2010;8:124–33.
27. Upchurch CP, Grijalva CG, Wunderink RG, et al. Community-acquired pneumonia visualized on CT scans but not chest radiographs: pathogens, severity, and clinical outcomes. Chest 2018;153:601–10.
28. Holm A, Nexoe J, Bistrup LA, et al. Aetiology and prediction of pneumonia in lower respiratory tract infection in primary care. Br J Gen Pract 2007;57:547–54.
29. Hopstaken RM, Muris JW, Knottnerus JA, Kester AD, Rinkens PE, Dinant GJ. Contributions of symptoms, signs, erythrocyte sedimentation rate, and C-reactive protein to a diagnosis of pneumonia in acute lower respiratory tract infection. Br J Gen Pract 2003;53:358–64.
30. Lieberman D, Shvartzman P, Korsonsky I, Lieberman D. Diagnosis of ambulatory community-acquired pneumonia. Comparison of clinical assessment versus chest X-ray. Scand J Prim Heal Care 2003;21:57–60.
31. Steurer J, Held U, Spaar A, et al. A decision aid to rule out pneumonia and reduce unnecessary prescriptions of antibiotics in primary care patients with cough and fever. BMC Med 2011;9:56.
32. Wipf JE, Lipsky BA, Hirschmann JV, et al. Diagnosing pneumonia by physical examination: relevant or relic? Arch Intern Med 1999;159:1082–7.
33. Diehr P, Wood RW, Bushyhead J, Krueger L, Wolcott B, Tompkins RK. Prediction of pneumonia in outpatients with acute cough-A statistical approach. J Chronic Dis 1984;37:215–25.
34. Gonzalez Ortiz MA, Carnicero Bujarrabal M, Varela Entrecanales M. Prediction of the presence of pneumonia in adults with fever. Med Clin (Barc) 1995;105:521–4.
35. Saldías PF, Díaz FA, Cabrera TD, Gederlini GA, De Solminihac LI, Hernández AP. Predictive value of history and physical examination for the diagnosis of community-acquired pneumonia in adults. Rev Med Chil 2007;135:143–52.

Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13965/full

Data Supplement S1. Supplementary material.