Office of Evidence Based Practice (EBP) – Critically Appraised Topic: Clinical Features of Atypical Community Acquired Pneumonia

Specific Care Question

In pediatric patients with suspected CAP, what clinical features suggest atypical pneumonia?

Recommendations from the CAP Clinical Practice Guideline (CPG) Team

There are no strong clinical features to differentiate atypical pneumonia from other organisms. The overall certainty in the evidence is moderate[d] (see Summary by Symptom for substantiation of recommendations).

Overall there is moderate certainty in the evidence reported by Wang et al. (2012) who stated M. pneumoniae cannot be diagnosed based on signs and symptoms. Wang et al. (2012) reported the prevalence of M. pneumoniae at 10% to 36%. Although absence of wheeze is 12% more likely in patients with M. pneumoniae, if treatment was based on lack of this symptom, 61% to 89% would not have M. pneumoniae, and 25% of children infected with M. pneumoniae would not be properly treated (Wang et al., 2012). The more recent trials do not have the rigor of Wang (2012) and do not change the certainty that signs and symptoms can predict atypical pneumonia.

Literature Summary

Background Symptoms and clinical features of community acquired pneumonias overlap, and are not reliable in characterizing viral, bacterial, and atypical pneumonias (Kavanagh, 2018). Approximately 80% of pneumonias are of viral origin (Bradley et al., 2011, p e38). Of the remaining cases of bacterial origin, 3-23% were atypical pneumonias (Bradley et al., 2011, p. e38). Some pneumonias are classified as atypical because (a) they present with milder symptoms, (b) the symptoms have a longer duration, (c) chest radiographs may have a different appearance, and (d) the usual antibiotic used to treat typical pathogens are not effective (CDC, 2018).

The most common bacteria responsible for atypical pneumonias are *Chlamydophila pneumoniae (C. pneumoniae)* in infants and *Mycoplasma pneumoniae (M. pneumoniae)* in older children, (Bradley et al., 2011, p. e39). The Infectious Diseases Society of America (IDSA) makes a strong recommendation based on high-quality evidence that diagnostic testing for *C. pneumoniae* should not be performed because laboratory tests to confirm this diagnosis do not exist (Bradley et al, 2001, p. e28).

In a sample of 2,638 children in the United States, *M. pneumoniae* was more common in children greater than 5-years of age (Jain et al., 2015). The (IDSA) makes a weak recommendation, based on moderate quality evidence, that children with signs and symptoms suspicious for *M. pneumoniae* should be tested to help guide antibiotic selection (Bradley et al., 2011, p. e28). IDSA delineates the signs and symptoms of atypical pneumonias as: (a) slowly progressing symptoms, (b) malaise, (c) sore throat, (d) low grade fever, and (e) cough that develops over 3 to 5 days. This review will summarize identified literature to determine if any of these symptoms are valid or reliable symptoms to guide the clinician to tests for *M. pneumoniae* to guide antibiotic selection.

Study characteristics. The search for suitable studies was completed on October 16, 2018. F. Turcotte Benedict, MD, MPH, FAAP and S. Brackett, APRN reviewed the 124 titles and/or abstracts found in the search and identified 11 articles believed to answer the question. Two additional articles were identified by an ancestry search. After an in-depth review three articles answered the question (Guo, Wang, Zhu, & Hao, 2015; Medjo et al., 2014; Wang et al., 2012) The studies included one systematic review of seven diagnostic test accuracy studies (Wang et al., 2012) and two cohorts (Guo et al., 2015; Medjo et al., 2014).

Wang et al. (2012) was a well-done SR/MA (Higgins & Green, 2011), but the included studies exhibited inconsistency, indirectness, and imprecision. An example of inconsistency was various methods were used to confirm the diagnosis of *M. pneumoniae*, since there is no gold standard. Tests employed for diagnosis included (a) IgM serology on a single blood sample, (b) antigen detection in a nasopharyngeal aspirate, (c) single antibody titer, or (d) PCR analysis of respiratory secretions. An example of indirectness was that baseline study populations were different, some studies tested for *M. pneumoniae* to be included in the sample, while others did not. Finally, imprecision was exhibited by 20-50-fold differences in specificity values from individual studies. The range of specificities for the symptom fever ranged from 0.02 to 0.43. The evidence from Wang et al. (2012) was reported as moderate certainty.

The other studies are of low certainty. Since Guo, Wang, Zhu, and Hao (2015) was retrospective cohort study, and Medjo et al. (2014) was prospective cohort study and neither had. Both were designed to determine if clinical, radiological, or laboratory tests could guide the accuracy of the diagnosis of *M. pneumoniae*. Neither study had findings that could be added to the sensitivity and specificity 2X2 tables reported in Wang et al. (2012).

Summary by Symptom

Wheeze. Three studies (Guo et al., 2015; Medjo et al., 2014; Wang et al., 2012) measured wheeze (*N* =1952). Wang et al. (2012) is a systematic review/meta-analysis (SR/MA) of diagnostic tests accuracy. It included seven trials (Agarwal, Awasthi, Rajput, Tiwari, & Jain, 2009; Chan, Lum, Ngeow, & Yasim, 2001; Kumar, Saigal, & Sethi, 2011; Maheshwari, Kumar, Sethi, & Bhalla, 2011; Prapphal et al., 2006; Principi, Esposito, Blasi, Allegra, & Mowgli study, 2001; Somer, Salman, Yalcin, & Agacfidan, 2006) for this symptom. The findings were presented as pooled sensitivities and specificities *(n* = 1698). Table 1 contains the pooled data, along with positive and negative likelihood ratios. Although the symptom "absence of wheeze" was a statistically significant diagnostic factor for atypical pneumonia, it was not clinically significant (Wang, et al., 2012). If CAP patients without wheeze were treated with antibiotic for *M. pneumoniae*, the range of patients who would be treated who did not have CAP would be 61-89%. Furthermore, appropriate antibiotic treatment would have been missed in 25% of patients with CAP who did wheeze and were *M. pneumoniae* positive by serology or culture (Wang, et al., 2012).

The other included studies could not be added to the pooled results for sensitivity and specificity symptoms for the diagnosis of atypical CAP (see Table 2). Guo et al. (2015) and Medjo et al. (2014) included a total of 254 subjects. Guo et al. (2015) reported 4.3% (3/70) of patients with atypical CAP wheezed, while 44% (8/18) of those with viral pneumonia wheezed ($p < .0001$). Medjo et al. (2014) reported 33% (8/24) of those with *M. pneumoniae* CAP had a wheeze and 15% (22/142) of those with non-*M. pneumoniae* CAP wheezed.

Cough. Three studies (Guo et al., 2015; Medjo et al., 2014; Wang et al., 2012) are included for the symptom of cough (n = 1695). Wang et al. (2012) reported the pooled sensitivity, specificity, positive and negative likelihood ratios from five studies (Agarwal et al., 2009; Kumar et al., 2011; Prapphal et al., 2006; Principi et al., 2001; Somer et al., 2006) for this symptom. Wang et al. (2012) reported the symptom of cough had a sensitivity of 89% but the specificity for indicating *M. pneumoniae* was poor (15%). (see Table 1). Guo et al., (2015) reported subjects with and without *M. pneumoniae* had a cough 60% of the time, while (Medjo et al., 2014) reported cough symptoms were present 83% of the time in those with *M. pneumoniae* versus 39% of the time in those without *M. pneumoniae* (see Table 2).

Other symptoms. Coryza, crepitations/rales were other symptoms studied. Wang et al. (2012) included four trials (Kumar et al., 2011; Maheshwari et al., 2011; Principi et al., 2001; Somer et al., 2006) for coryza and five studies for crepitations (Agarwal et al., 2009; Maheshwari et al., 2011; Prapphal et al., 2006; Principi et al., 2001; Somer et al., 2006). Coryza was not a useful indicator, noted by the pooled LR+ and LR- in Table 1. Crepitations were sensitive, but not a specific indicator of *M. pneumoniae*. From Guo et al. (2015) and Medjo et al. (2014) coryza was present in 99% or 100% of those with *M. pneumoniae* and 99% or 89% in those without *M. pneumoniae*, respectively. Medjo et al. (2014) reported on rales (not crepitations) and found 17% of subjects with *M. pneumoniae* and 33% of subjects without *M. pneumoniae* had rales. Guo et al. (2015) did not report on this symptom (see Table 2).

Identification of Studies

Search Strategy and Results (see Figure 1)

PubMed

(("community acquired pneumonia"[All Fields] OR "community-acquired pneumonia"[All Fields] OR ("Community-Acquired Infections"[MeSH] AND "Pneumonia"[MAJR])) AND ("Signs and Symptoms"[Mesh] OR "clinical prediction"[All Fields] OR "clinical features"[All Fields] OR "atypical pneumonia"[All Fields] OR "Pneumonia, Mycoplasma"[Mesh])) AND (child OR children OR infant OR adolescence OR pediatr* OR paediatr*) AND ("last 5 years"[PDat])

Records identified through database searching *n* = 124

Records identified through other sources *n* = 2

Studies Included in this Review

Citation	Study Type
*Agarwal, Awasthi, Rajput, Tiwari, and Jain (2009)	Cohort
*Chan, Lum, Ngeow, and Yasim (2001)	Cohort
Guo et al. (2015)	Cohort
*Kumar, Saigal, and Sethi (2011)	Cohort
*Maheshwari, Kumar, Sethi, and Bhalla (2011)	Cohort
Medjo et al. (2014)	Cohort
*Prapphal et al. (2006)	Cohort
*Principi, Esposito, Blasi, Allegra, and Mowgli study (2001)	Cohort
*Somer, Salman, Yalcin, and Agacfidan (2006)	Cohort
Wang et al. (2012)	SR/MA

Note: * Included in SR/MA

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Arfaatabar et al. (2018)	Does not answer the question
Jain et al. (2015)	Epidemiologic information
Rodriquez de Ita et al. (2014)	Does not answer the question
Saraya et al. (2018)	Includes the wrong population
Shu et al. (2015)	Article is not in English
Sondergaard, Friis, Hansen, and Jorgensen (2018)	Does not answer the question
Sun et al. (2015)	Does not answer the question
Zhao, Chen, Yang, and Deng (2016)	Article is not in English

Methods Used for Appraisal and Synthesis

[a]Rayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).

[b]Review Manager (Higgins & Green, 2011) is a Cochrane Collaborative computer program used to assess the study characteristics as well as the risk of bias and create the forest plots found in this analysis.

[c]The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the process in which literature is searched, screened, and eligibility criteria is applied (Moher, Liberati, Tetzlaff, & Altman, 2009).

[a]Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews, 5*(1), 210. doi:10.1186/s13643-016-0384-4

[b]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cochrane Collaboration, 2011.

[c]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 **For more information, visit www.prisma-statement.org.**

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Acronyms Used in this Document

Acronym	Explanation
APRN	Advanced Practice Nurse
CAP	Community Acquired Pneumonia
CDC	Centers for Disease Control
CI	Confidence Intervals
CRP	C-reactive Protein
FAAP	Fellow of the American Academy of Pediatrics
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IDSA	Infectious Diseases Society of America
MPH	Master of Public Health
OR	Odds Ratio
QAUDUS-2	Quality Assessment of Diagnostic Accuracy Studies-2
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SD	Standard Deviation
SR/MA	Systematic Review/Meta-analysis
WBC	White Blood Cell

Date Developed/Updated
June 2019

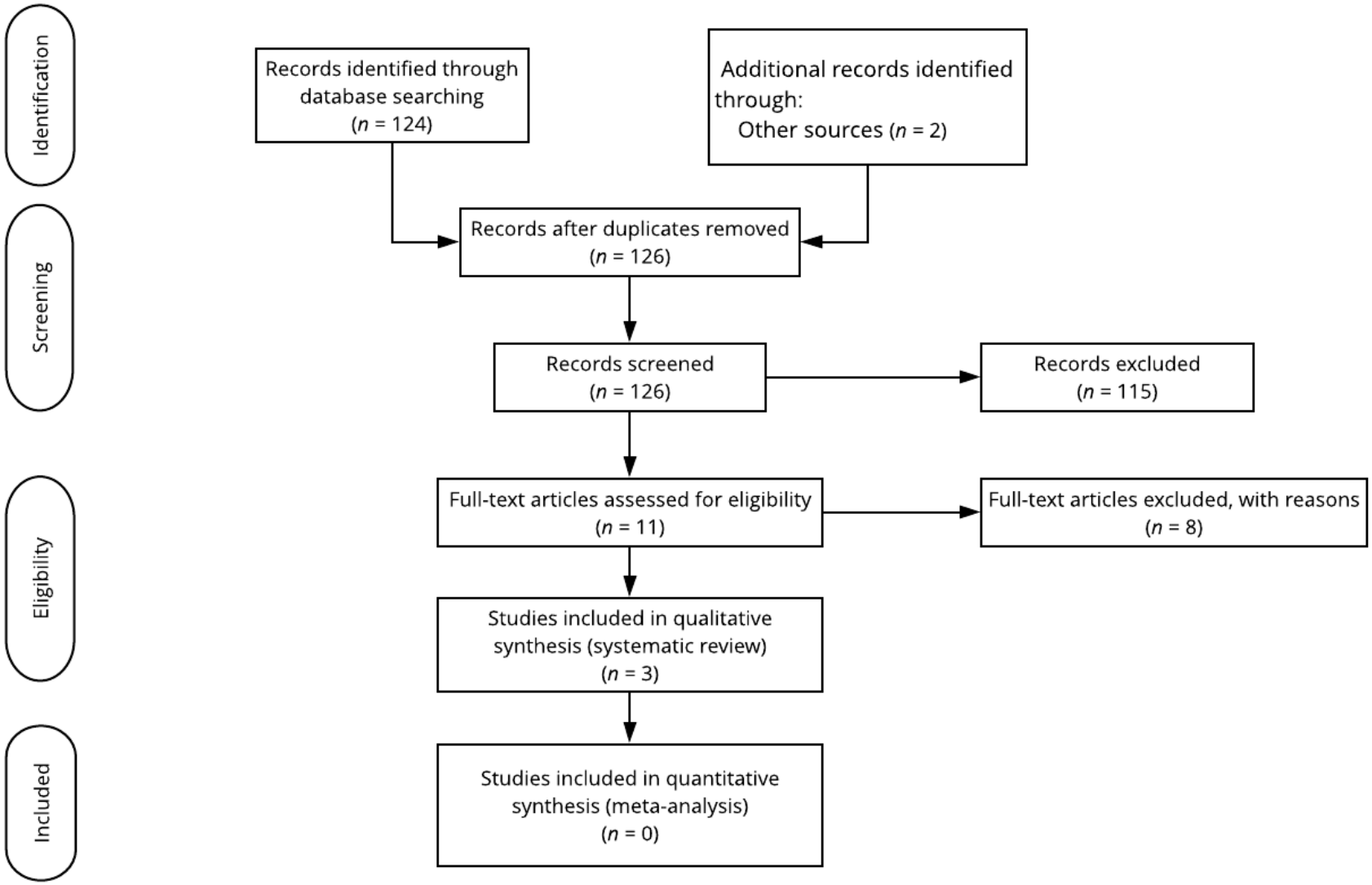


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)[e]

Table 1

Pooled Sensitivity, Specificity, Positive Likelihood Ratio, and Negative Likelihood Ratio of CAP Symptom for the Diagnosis of M. pneumoniae

Symptom, *n* = number of studies	Sensitivity, [95% CI]	Specificity, [95% CI]	Positive likelihood ratio, [95% CI]	Negative likelihood ratio, [95% CI]
Cough, n= 5	.89, [.67, .97]	.15, [.05, .37]	1.04, [0.95, 1.13]	0.78, [0.44, 1.39]
Wheeze n = 6	.25, [.17, .36]	.67, [.56, .76]	.76, [.67, .97]	1.12, [1.02, 1.23]
Coryza n= 4	.32, [.08, 072]	.66, [.28, .91]	0.95, [0.71, 1.26]	1.03, [0.9, 1.17]
Crepitations n = 5	.84, [078, .88]	.22, [.14, .32]	1.06, [0.96, 1.18]	0.77, [0.52, 1.12]

(Wang et al., 2012)

Table 2

Clinical Signs and Symptoms of Subjects With and Without M. pneumoniae Pneumonia

Study	Guo 2015	Medjo 2014
Subjects (*N* =)	88	166
Number with *M. pneumoniae*	70	24
With *M. pneumoniae (%)*		
Wheeze	4.3	33
Cough	60	83
Coryza	99%	100
Rales	Did not report	17
Without *M. pneumoniae (%)*		
Wheeze	44	8
Cough	60	39
Coryza	99	89
Rales	Did not report	33

(Guo et al., 2015; Medjo et al., 2014)

Characteristics of Studies

Guo 2015

Methods	Retrospective case study
Participants	**Participants:** Pediatric patients with CAP, with lobe or multi foci infiltration **Setting:** Retrospective chart review of CAP cases at a large university teaching hospital (Soochow University, Suzhou, China) between May 2012 and April 2013 **Number enrolled into study:** *N* = 126 consecutive cases • Proven viral or mycoplasma CAP: *n* = 88 cases **Gender, males:** *n* = 71 (56%) **Age, years [range]:** 4 [11 days to 14 years] **Inclusion criteria:** • Previously healthy children with radiologically confirmed lobar or multi focal lung infiltrates ○ Lobar distribution defined as involvement of a single lobe ○ Two or more foci (unilateral or bilateral) was considered multi focal ○ Radiographic findings were independently reviewed by two radiologists; differences in diagnosis conclusions was reached through consensus resolution • Diagnosis of CAP ○ Mycoplasma pneumonia diagnosis defined as acute respiratory disease with abnormal chest radiograph findings and positive laboratory tests combined with real-time PCR using DNA extracted from nasopharyngeal swab specimens ○ Viral pneumonia diagnosis defined as acute respiratory disease with abnormal chest radiograph findings and positive viral growth (including influenza A and B; adenovirus; respiratory syncytial virus; bocavirus; human metapneumovirus; and parainfluenza virus 1, 2, and 3) from respiratory cultures obtained from either nasopharyngeal swab or bronchial-aspirate sampling ○ Medical charts, radiographs, and laboratory findings were retrospectively reviewed by both a respiratory physician and radiologist **Exclusion criteria:** • History of asthma • Patients with simultaneous viral and mycoplasma infections **Covariates identified to influence diagnosing atypical pneumonia:** • Increased respiratory rate (p = .0053) • Wheeze (p < .0001) • Gender, males (p = .0197) • Increased lymphocyte percentage (p = .0184)
Interventions	• Factors analyzed included fever; wheeze; increase of respiratory rate; cough; CRP; white blood cell count (WBC); and radiological findings among three different age groups: 0 to 23 months, 2 to 4 years, and older than 5 years

Outcomes

Primary outcome(s):

- Factors allowing differential diagnosis of viral and mycoplasma CAP with lobe or multi foci infiltration

Results

CAP cases:

- *M. pneumoniae*: *n* = 70
- Viral: *n* = 18
- Unknown: *n* = 38

Variables found to be more frequent in children with atypical pneumonia were further analyzed by logistic regression and the following were significantly associated with atypical pneumonia

Variable	Odds Ratio [OR]	95% Wald Confidence Interval [CI]	*p* value
Wheeze	.063	0.010 – 0.271	$p < .0001$
Increased respiratory rate	.093	0.013 – 0.653	$p = .0095$
Increased lymphocyte %	.053	0.012 – 0.337	$p = .0027$

Medjo 2014

Methods	Prospective, cohort study to assess the incidence of *Mycoplasma pneumoniae* pneumonia to determine the clinical, radiological, and laboratory features specific for *M. pneumoniae* and to evaluate which diagnostic tests (serology, real-time polymerase chain reaction (RT-PCR) and culture) provide increased accuracy in the diagnosis of *M. pneumoniae*.
Participants	**Participants:** Previously healthy children aged between 1 and 15 years with symptoms, signs and chest radiographs consistent with community-acquired pneumonia **Setting:** University Children's Hospital Emergency Department in Belgrade, Serbia from April 2012 to March 2014 **Number enrolled into study:** *N* = 166 **Number completed:** *N* = 166 **Gender, males:** *N* = 86 **Age, years (mean, SD):** 6.35, 4.52 **Inclusion criteria:** • Aged between 1 and 15 years • Presence of fever, acute respiratory symptoms (cough, tachypnea, difficult breathing) or both, and a new infiltrate on chest radiography or a consolidation not attributable to some other etiology **Exclusion criteria:** • Children who received anti-mycoplasma therapy **Covariates identified to influence diagnosing *M. pneumoniae pneumonia*:** • Gender, males; *p* = .014 • Age, years—mean (SD); *p* = .001 • Fever duration before enrollment (days): *p* = .021 • Cough duration before enrollment (days): *p* = .026
Interventions	**Group 1:** Patients with *M. pneumoniae* pneumonia – Acute *M. pneumoniae* was defined if at least one method was positive among detection of *M. pneumoniae* by culture or by PCR or detection of *M. pneumoniae* -specific antibodies by serology **Group 2:** Patient with non- *M. pneumoniae* pneumonia
Outcomes	**Primary outcome(s):** • Variables identified from the logistic regression • Sensitivity and specificity of laboratory tests serology (IgM antibodies > 1.1 detected and fourfold increase of IgG antibodies) and RT-PCR
Results	Variables found to be more frequent in children with *M. pneumoniae* pneumonia were further analyzed by logistic regression and the following were significantly associated with *M. pneumoniae* pneumonia

Variable	Odds Ratio [OR]	95% Confidence Interval [CI]	*p* value
Headache	36.077	4.897 – 265.811	*p* = 0.001
Wheezing	5.681	1.776 – 18.175	*p* = 0.003
Male gender	.162	0.048 – 0.548	*p* = 0.003
Age 5 and older	3.067	1.016 – 9.251	*p* = 0.047

Sensitivity and specificity of laboratory tests
- Diagnostic values when using fourfold or greater increase of IgG antibody in paired sera as the gold standard

Test	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Serology (IgM antibodies)	81.82	100	100	97.30
RT-PCR	81.82	98.61	90	97.26

- Diagnostic values when using RT-PCR as the gold standard

Test	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Serology (IgM antibodies)	80	98.63	88.89	97.30
Serology (fourfold increase IgG antibodies)	90	97.26	81.82	98.61

Wang 2012

Design	Diagnostic Quantitative Synthesis and Meta-analysis
Objective	There were two objectives of this SR/MA. They are (a) to assess the diagnostic accuracy of the signs and symptoms of *M. pneumoniae* infection in children and adolescents, and (b) to assess the sources of heterogeneity.
Methods	**Protocol and registration.** It is a Cochrane systematic review and meta-analysis. It has gone through a development process from protocol to report. **Types of studies.** Published peer reviewed trials of diagnostic test accuracy that recruited subjects in a prospective and consecutive manner. The presence of *M. pneumoniae* confirmed by serology. Data had to be available to construct 2X2 tables. **Participants.** Children and adolescents aged less than or greater than 18 years with clinical or radiological diagnosis of CAP. Subjects were excluded if a co-morbidity was present, such as cystic fibrosis or bronchiectasis; HIV or immunosuppressant medication; **Index tests.** Clinical symptoms and signs including • Cough • Wheeze • Coryza • Crepitations • Fever (different definitions per each study) • Rhonchi • Shortness of breath • Chest pain • Diarrhea • Myalgia • Headache **Target Condition.** *M. pneumoniae* in children and adolescents with CAP **Reference Standards.** *M. pneumoniae* with or without the use of additional laboratory tests such as culture or PCR. Serology is the most used test. **Information sources.** There were no language or publication restrictions. • MEDLINE • EMBASE **Search.** An extensive search strategy is published in the paper's appendix. The electronic search was augmented by hand-searching references from the included studies reference lists. Medion database, Databases of Reviews of Effects 2012, and the Cochrane Register of Diagnostic Test Accuracy studies were searched. The list of included studies was reviewed by content experts to detect any studies that may have been omitted.

	Study Selection. Peer reviewed studies of any design which included subjects who were prospectively and consecutively enrolled into the study. Also, studies had to report data in enough detail to enable the construction of 2X2 tables. **Data collection process.** Two authors collected data independently. The following data was collected: study characteristics, where the study took place, health care setting, criteria for CAP diagnosis, and specifically *M. pneumoniae* diagnosis. All discrepancies were resolved with a third author. **Methodological quality (Risk of Bias)**. The QUADAS tool was the basis for the assessment of bias. **Summary measures.** • 2X2 table were constructed for each study. Presence of *M. pneumoniae* versus the presence of a clinical symptom or sign. **Synthesis of results.** • Included the prevalence of *M. pneumoniae* in the study population, and the influence on post-test probability of *M. pneumoniae.* • Pooled sensitivities, specificities, negative and positive likelihood ratios with 95% confidence intervals, if at least four studies were available for that sign or symptom. • Heterogeneity was explored evaluated by using mixed-effects logistic regression. • Covariates identified: age, health care setting, clinical versus clinical and radiological diagnosis, diagnosis of *M. pneumoniae* by serology, and other laboratory investigations.
Results	**Study Selection.** **Number of articles identified:** *N* = 8299 **Full-text articles assessed for eligibility:** *n* = 97 ○ **Studies included in qualitative synthesis:** *n* = 7 **Synthesis of results.** • Sensitivity & Specificity • + Likelihood ratio, and – Likelihood ratio • Prevalence of *M. pneumoniae* assessed at 10% to 36% **Methodological quality of included studies (Risk of Bias)**. • Overall methodological quality was strong. Exceptions include: ○ Five studies did not clearly report the exclusion of subjects with underlying co-morbidity, or immunocompromise • One study did not use a suitable reference standard for the diagnosis of *M. pneumoniae* • Explicit description of blinding of either index or reference test results was not found in any study • Delay between index tests and reference tests was not reported well in 5/7 studies.
Discussion	**Summary of evidence.** • Overall, the signs and symptoms of CAP are not reliable in diagnosing pneumonia caused by *M. pneumoniae*. • Pooled estimates for presence of *M. pneumoniae*: ○ Cough – Sensitive, but poorly specific

- Crepitations-Sensitive, but poorly specific
- Coryza- No better than chance
- Wheeze - Wheeze was 12% more likely to be absent in patients with *M. pneumoniae (pooled LR+* = 0.76, 95% CI 0.60 to 0.97; *pooled LR1- = 12*, 95% CI 1.02 to 1.23*)*.

	Pooled Sensitivity	95% CI	Pooled Specificity	95% CI
Cough	.89	[.67, .97]	.15	[.05, .37]
Crepitations	.84	[.78, .88]	.22	[.14, .32]
Coryza	.32	[.08, .72]	.66	[.28, .91]
Wheeze	.25	[.17, .36]	.67	[.56, .76]

- The following signs and symptoms could not be pooled and did not discriminate patients with or without *M. pneumoniae*:
  - Fever
  - Rhonchi
  - Shortness of breath
  - Headache
  - Chest pain
  - Diarrhea
  - Myalgia
- The strongest symptom is absence of wheeze. It is a statistically significant diagnostic indicator, but errors of classification can occur.
- Based on a prevalence of 10-36%
  - If empirical antibiotic were given to patients with CAP in whom wheeze was not reported, 61% to 89% would not have *M. pneumoniae* positive serology or culture.
  - Also, antibiotics would have been withheld from 25% of patients who were *M. pneumoniae* positive by serology or culture.

Limitations.

- Few studies, and low number of subjects.

Funding	**Funding.** The primary author is funded by the National Institute for Health Research (UK)

References

References marked with an asterisk indicate studies included from the meta-analysis.

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