Children's Mercy KANSAS CITY
Evidence Based Practice

Critically Appraised Topic (CAT): Procalcitonin in Bacterial Pneumonia

Specific Care Question

In pediatric patients with suspected community acquired pneumonia, what is the diagnostic accuracy of procalcitonin (PCT) in predicting bacterial pneumonia?

Rationale for Question Asked

The current challenge in diagnosing bacterial pneumonia in children is the need for a fast, reliable test to help determine if antibiotic treatment is indicated. Evaluating PCT's diagnostic accuracy is needed to determine if the test could assist providers in effectively stratifying risk of bacterial disease and making informed treatment decisions. As PCT testing becomes more accessible, a comprehensive literature review is needed to ensure optimal test ordering practices and interpretation in this specific patient population.

Overview and Certainty of Evidence

Two systematic reviews and meta-analyses were identified to evaluate PCT testing for diagnosing bacterial pneumonia in children (Gunaratnam et al., 2021; Tsou et al., 2020). While both studies demonstrated a moderate ability of PCT to distinguish bacterial from nonbacterial pneumonia (AUROC 0.67-0.71), limitations were identified. Sensitivity ranged from 53% to 69%, indicating the potential for missing true positive cases. Specificity ranged from 60% to 73%, suggesting the possibility of misclassification. Additionally, variations in PCT testing methodology and interpretation were noted across studies. Publication bias was also a potential concern in one review. Overall, PCT testing holds promise as a diagnostic aid, but due to the moderate sensitivity and specificity, it should be used in conjunction with other clinical information for optimal patient management.

Gunaratnam et al., 2021

A systematic review and meta-analysis were conducted to evaluate the diagnostic accuracy of 23 biomarkers for pediatric patients (*n* = 1543, birth to 18 years) with suspected bacterial pneumonia, as detailed in Table 1. The primary focus was differentiating bacterial from nonbacterial causes (Gunaratnam et al., 2021). PCT emerged as one of the better-performing biomarkers, exhibiting an area under the receiver operating characteristic curve (AUROC) of 0.70 (95% CI: 0.67-0.74). However, PCT demonstrated moderate sensitivity (0.69, 95% CI: 0.65-0.77) and specificity (0.64, 95% CI: 0.58-0.68) with an optimal cut-off of 0.59 ng/mL. While the AUROC suggests some potential for PCT in distinguishing bacterial from nonbacterial pneumonia, the moderate sensitivity and specificity indicate limitations in its use as a standalone diagnostic tool in clinical practice (Gunaratnam et al., 2021).

> **Certainty Of The Evidence** Certainty of evidence is based on what the authors of the meta-analysis reported. The authors assessed the risk of bias using the QUADAS-2 tool to evaluate the quality of the diagnostic studies. Of the 31 studies, 15 were determined to have a high or unclear risk of bias for the reference standard. There is no definitive reference standard for diagnosing bacterial pneumonia. For this review, the authors determined that studies using microbiological evidence and chest radiography findings were considered to have a lower risk of bias. Additionally, 15 of the 31 studies lacked clarity in patient selection and how the index test was interpreted. Finally, the authors reported that some studies had concerns regarding their applicability based on patient selection (5 of the 31 studies), the reference standard used (9 of the 31 studies), or the inclusion of only specific types of pneumonia.

Tsou et al., 2020

Tsou et al. (2020) conducted a systematic review and meta-analysis of 25 observational studies (*n* = 2864, birth to 21 years) investigating children with symptoms suggestive of pneumonia (Table 2). The analysis focused on diagnosing bacterial pneumonia using AUROC. The AUROC ranged from 0.67 to 0.71, indicating moderate differentiation between bacterial and nonbacterial cases. A cut-off of 0.5 ng/mL yielded an AUROC of 0.68 (95% CI: 0.64-0.72) but with moderate sensitivity (0.68, 95% CI: 0.50-0.82) and specificity (0.60, 95% CI: 0.47-0.72). Increasing the cut-off to 1.0 ng/mL improved specificity to 0.64 (95% CI: 0.54-0.73) but decreased sensitivity to 0.61 (95% CI: 0.43-0.77). The highest cut-off (2.0 ng/mL) achieved the best specificity (0.71, 95% CI: 0.58-0.81) but at the cost of the lowest sensitivity (0.59, 95% CI: 0.40-0.71). Despite the moderate AUROC suggesting some potential, the limited sensitivity and specificity highlight the inadequacy of PCT as a standalone diagnostic tool for bacterial pneumonia in clinical practice (Tsou et al., 2020).

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< **5 years of age.** For children younger than 5 years, Tsou et al. (2020) analyzed the diagnostic accuracy of PCT for bacterial pneumonia using AUROC (number of studies = 9, patient count not reported). PCT demonstrated moderate performance (AUROC = 0.69, 95% CI: 0.65-0.73) in diagnosing this age group. However, similar to the overall analysis, sensitivity (0.53, 95% CI: 0.38-0.67) and specificity (0.73, 95% CI: 0.62-0.82) were moderate. These findings again suggest that while PCT shows promise in differentiating bacterial from nonbacterial pneumonia, it is insufficient for sole reliance in clinical diagnosis (Tsou et al., 2020).

Certainty Of The Evidence. Certainty of evidence is based on what the authors of the meta-analysis reported. The authors of this meta-analysis evaluated the certainty of the evidence using the QUADAS-2 tool to assess the quality of the included studies. While they found a low overall risk of bias and applicability concerns (only 5 out of 25 studies rated high risk in any category), some limitations exist. The studies used different methods to diagnose bacterial pneumonia, potentially leading to misclassification bias. Significant variation existed across the PCT testing systems used, introducing inconsistency. The authors acknowledged that the types of bacteria causing pneumonia can differ by age group, contributing to further variation in results. An asymmetrical Deke's funnel plot suggested potential publication bias, meaning studies with negative findings might be less likely to be reported.

Table 1. PCT Meta-analysis Summary
Gunaratnam et al., 2021

N (number of patients)	Youden Index Cutoff	AUROC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
N = 1543	0.59 ng/mL	0.70 (0.67, 0.74)	0.69 (0.65, 0.77)	0.64 (0.58, 068)

Table 2. Meta-analysis and Subgroup Analysis
Tsou et al., 2020

Variable	N (studies)	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	AUROC (95% CI)	I^2 (95% CI)
Bacterial Pneumonia	21	0.64 (0.54, 0.74)	0.72 (0.64, 0.79)	2.30 (1.8, 3.0)	0.5 (0.38, 0.65)	0.74 (0.7, 0.78)	99 (98, 99)
0.5 ng/ml	11	0.68 (0.50, 0.82)	0.6 (0.47, 0.72)	1.7 (1.3, 2.2)	0.53 (0.34, 0.81)	0.68 (0.64, 0.72)	99 (98, 99)
1.0 ng/ml	9	0.61 (0.43, 0.77)	0.64 (0.54, 0.73)	1.7 (1.2, 2.3)	0.60 (0.39, 0.93)	0.67 (0.62, 0.71)	97 (95, 99)
2.0 ng/ml	8	0.59 (0.40, 0.76)	0.71 (0.58, 0.81)	2 (1.3, 3.2)	0.58 (0.36, 0.93)	0.71 (0.67, 0.75)	95 (98, 99)
Typical vs Non-typical	12	0.78 (0.64, 0.88)	0.66 (0.51, 0.78)	2.3 (1.6, 3.3)	0.33 (0.19, 0.56)	0.78 (0.74, 0.82)	98 (97, 99)
0.5 ng/ml	6	0.77 (0.51, 0.91)	0.58 (0.42, 0.72)	1.8 (1.5, 2.2)	0.4 (0.2, 0.82)	0.69 (0.65, 0.73)	97 (96, 99)
1.0 ng/ml	6	0.57 (0.36, 0.75)	0.65 (0.52, 0.76)	1.6 (1.1, 2.4)	0.67 (0.43, 1.05)	0.65 (0.61, 0.69)	94 (89, 99)
Typical vs atypical	4	0.75 (0.65, 0.83)	0.48 (0.23, 0.74)	1.5 (0.8, 2.6)	0.51 (0.25, 1.04)	0.75 (0.71, 0.79)	85 (68, 100)
1.0 ng/ml	4	0.6 (0.47, 0.71)	0.54, (0.28, 0.79)	1.3 (0.6, 2.7)	0.74 (0.36, 1.52)	0.60 (0.56, 0.65)	81 (59, 100)
Age less than 5 years	9	0.53 (0.38, 0.67)	0.73 (0.62, 0.82)	2.00 (1.3, 3.1)	0.64 (0.46, 0.89)	0.69 (0.65, 0.73)	97 (95, 99)

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Identification of Studies
Search Strategy and Results

#12
#6 AND **#10**

#11
#5 AND **#10**

#10
([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim) AND (**'article'**/it OR **'article in press'**/it OR **'preprint'**/it) AND [2010-2023]/py

#9
#6 AND **#7**

#8
#5 AND **#7**

#7
(**'pediatrics'**/exp OR **pediatr***:ti,ab,kw OR **'pediatric'**/exp OR **paediatr***:ti,ab,kw OR **'child'**/exp OR **child**:ti,ab,kw OR **'children'**/exp OR **children**:ti,ab,kw OR [adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim) AND (**'article'**/it OR **'article in press'**/it OR **'preprint'**/it) AND [2010-2023]/py

#6
#1 AND **#3** AND **#4**

#5
#1 AND **#2** AND **#4**

#4
'diagnostic'/exp OR **'diagnostic'**:ti,ab,kw OR **'diagnosis'**/exp OR **'diagnosis'**:ti,ab,kw OR **'diagnostic accuracy'**/exp OR **'sensitivity and specificity'**/exp OR **'sensitivity and specificity'** OR **'sensitivity'**/exp OR **'sensitivity'**:ti,ab,kw OR **'predictive value'**/exp OR **'differential diagnosis'**/exp OR **'differential diagnosis'**:ti,ab,kw OR **'specificity'**/exp OR **'specificity'**:ti,ab,kw

#3
'bacterial pneumonia'/exp OR **'bacterial pneumonia'**:ti,ab,kw OR **'community acquired pneumonia'**/exp OR **'community acquired pneumonia'**:ti,ab,kw OR **'pneumonia'**/exp OR **pneumonia**:ti,ab,kw OR **'virus pneumonia'**/exp OR **'viral pneumonia'**:ti,ab,kw OR **'lower respiratory tract infection'**/exp

#2
'sepsis'/exp OR **sepsis**:ti,ab,kw OR **septic**:ti,ab,kw

#1 **'procalcitonin'**/exp OR **procalcitonin**:ti,ab,kw OR **'procalcitonin blood level'**/exp

Search Dates: 2013-2023
Records identified through database searching *n* = 581
Additional records identified through other sources *n* = 4
Records excluded due to not answering PICOT question *n* = 583

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Gunaratnam et al. (2021)

Design	**Diagnostic Quantitative Synthesis and Meta-analysis**
Objective(s)	To assess the ability of biomarkers to correctly identify bacterial pneumonia in children who present with respiratory distress

Methods	**Criteria for considering studies for this review**
	• **Types of studies:** Any diagnostic research study with a control group and at least one comparison group
	• **Participants:**
	  ○ Children, birth to 18 years of age
	  ○ Studies with adults were included if the results for children could be extracted
	• **Index test (new test):** Procalcitonin (PCT)
	• **Reference standard (gold standard test):**
	  ○ There is no gold standard test for the diagnosis of bacterial pneumonia
	  ○ Review authors used the reference standard of plausible microbiological evidence and a chest radiograph
	• **Target Condition(s):**
	  ○ Bacterial pneumonia
	
	Search methods for identification of studies
	• **Electronic databases searched:**
	  ○ Medline (1946 to May 2020)
	  ○ EMBASE (1974 to May 2020)
	  ○ CENTRAL (inception to May 2020)
	  ○ Global Health (1920 – 2020)
	• **Search strategy employed:**
	  ○ A librarian-directed search was conducted of the electronic databases in May 2020 (Search terms were provided [Supplementary Figure 2.])
	  ○ Ongoing trials were sought at ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (search performed August 2018, though could not be updated in 2020 as the portal was temporarily unavailable due to COVID-19)
	  ○ There were no language or format restrictions
	• **Searching other resources (such as reference list):**
	  ○ Reference lists of included articles were hand-searched
	
	Data collection and analysis
	• **Inclusion criteria:**
	  ○ Diagnostic research studies with a control group and at least one comparison group
	  ○ Studies that focused on children, birth to 18 years of age, meeting the target condition
	  ○ Adult studies meeting the target condition only if the results for children could be extracted
	  ○ Studies of any biomarker, defined as biological molecules found in an easily accessible bodily fluid which has the potential to serve as a measurable indicator of bacterial pneumonia
	  ○ Studies that had a cut-off value or an AUROC for the biomarker
	  ○ Studies that compared biomarker results in presumed bacterial pneumonia to results in other causes of respiratory distress
	  ○ Studies that stated the criteria for defining bacterial pneumonia and the rationale for including or excluding cases due to *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*
	• **Exclusion criteria:**
	  ○ Studies including adults if the results for children could not be extracted
	  ○ Studies that looked solely at bronchoalveolar lavage fluid
	• **Population:** Children, birth to 18 years of age, presenting in respiratory distress

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	• **Prior testing:** Not reported
	• **Setting:** Not reported a priori; below results are suggestive of findings
	  ○ Hospital setting (emergency department, admitting ward, pediatric intensive care)
	  ○ One study was conducted in an outpatient clinic in Tanzania
	  ○ One study did not identify the setting
	• **Study Design:** Systematic review/meta-analysis of 31 studies
	• **Data collection process:**
	  ○ Two independent reviewers screened the articles for inclusion, first by title and abstract, then by full text
	  ○ Disagreements were resolved by consensus
	  ○ Two investigators extracted data pertaining to study design, clinical setting, participants, target condition, reference standards, index test, cut-off values, comparator test(s), and outcomes (sensitivities and specificities) onto a standardized form
	  ○ Disagreements were resolved by consensus between the two reviewers
	• **Assessment of the certainty of the evidence-** Two investigators assessed each study for risk of bias and applicability using QUADAS-2.
	  ○ Studies that used plausible microbiological evidence in addition to chest radiograph findings were considered to have a low risk of bias
	  ○ Studies that did not use microbiological and chest radiograph findings were considered to have a high risk of bias
	  ○ Disagreements were resolved by consensus
	• **Data Synthesis (what statistical plan do the authors establish a priori):**
	  ○ **Cut offs:**
	  ○ A nonparametric approach was used to estimate an overall ROC curve using the information of all cut-off points available in the selected original studies, based on weighting each interpolated ROC curve
	  ○ Statistically optimal cut-off values of a biomarker were defined as the value where the Youden index is maximized and used a parametric method to define the threshold
	  ○ 0.5 – 2 ng/mL, with the exception of two studies, which used cut-offs of 0.18 ng/mL and 7 ng/mL.
	  ○ **Sensitivity:**
	  ○ Random-effects models were used to estimate optimal sensitivity (Youden index)
	  ○ Bootstrapping (1000 iterations) was used to estimate the 95% confidence intervals
	  ○ **Specificity:**
	  ○ Random-effects models were used to estimate optimal specificity (Youden index)
	  ○ Bootstrapping (1000 iterations) was used to estimate the 95% confidence intervals
	  ○ **Heterogeneity**: Not specifically addressed
	  ○ **ROC:**
	  ○ ROC curves were generated using a meta-analytic approach. The Martinez-Camblor (nsROC package) method was used to synthesize ROC curves from multiple diagnostic studies
	  ○ A random-effects model was used to estimate the overall AUROC
	  ○ **Publication bias:** Funnel plots of the diagnostic odds ratio for each of the biomarkers were created using the package *meta* in the R Statistical environment (https;//www.R-project.org).

Results	**Study Selection** **Number of articles identified:** *N* = 2342 **Full-text articles assessed for eligibility:** *n* = 157 ○ **Studies included in qualitative synthesis:** *n* = 31 observation studies

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- Four were retrospective; 27 were prospective
- Fifteen investigated PCT as an index test (14 were prospective observational studies; one was a retrospective observational study)

- **Studies included in quantitative synthesis:** *n* = 14 (PCT)
  - Thirteen prospective observational studies; 1 retrospective observational studies)
  - Study settings were the emergency department, hospital, and outpatient clinics
  - Studies were conducted in China, Finland, France, Italy, Switzerland, Tanzania, and the United States (the country was unclear in one study)
  - Defined as any of the following alone or in combination:
    - Having a chest radiograph with linear and patchy densities in a lacy pattern.
    - Based on chest radiographs and viral studies
    - Based on nasopharyngeal aspirate negativity for viral culture, PCR, or viral serology
    - Based on the absence of IgG antibodies to parainfluenza viruses type 1 and 3, influenza A and B viruses and adenoviruses, IgG and IgM antibodies to cytomegalovirus, and IgG antibodies to RSV or hMPV
    - Based on abnormal chest radiograph
    - Based on serological testing and nasopharyngeal swab results
    - Based on the absence of a single viral antigen detected in nasopharyngeal aspirate or a four-fold rise in serology to one virus only
    - Based on serology alone
    - Based on the absence of a single or multiple viral pathogens identified via nasopharyngeal swabs or oropharyngeal swabs for viral DFA and culture

Synthesis of quality of evidence (strength of evidence)

- Based on summarized results specific to the investigation of PCT
  - Four studies lacked clarity in patient selection
  - Three studies had a high risk of bias in the way the index test was interpreted
  - Three studies had a high risk of bias for the reference standard as only a chest radiograph or microbiological testing (rather than both) was used to define the condition.
  - In two studies, it was unclear if the reference standard was interpreted without knowledge of the results.
  - Seven studies had a high risk of bias with respect to flow and timing; most often, the studies excluded patients with evidence of both viral and bacterial pneumonia, no known pathogen, the "uncertain group," "equivocal group," or complicated pneumonia.
  - In two studies, it was unclear whether patients were excluded when there was evidence of viral and bacterial pneumonia, no known pathogen, or complicated pneumonia.
  - Regarding applicability, one study had concerns based on patient selection, including only patients in intensive care
  - In four studies, there were concerns regarding the applicability of the reference standard, as only pneumococcal pneumonia was included.

Synthesis of quantitative evidence

- **Sensitivity:** 0.69 (0.65 – 0.77)
- **Specificity:** 0.64 (0.60 – 0.68)
- **Heterogeneity:** Not explicitly addressed, though reported as a possible limitation in the review discussion
- **ROC:** AUROC 0.70 (0.67 – 0.74), Youden index 0.59 ng/mL (optimal cut-off value)
- **Publication bias:** Visual inspection of funnel plots did not reveal obvious asymmetry to suggest publication bias

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Discussion	**Limitations**
	• The review authors identified there was a lack of a gold standard (reference standard) for bacterial pneumonia
	• There was variability as to whether atypical bacterial infections were included within the definition of bacterial pneumonia, resulting in challenges when comparing individual study results due to heterogeneity
	• Studies included in the review were completed before pneumococcal vaccines were routinely offered, suggesting that biomarkers would perform differently if there were a lower prevalence of pneumococcal pneumonia
	• The method used for summary curves presented two limitations:
	  ○ Different studies were used to generate different curves for different biomarkers, resulting in the inability to compare the diagnostic accuracy of one biomarker to another using the area under the curves
	  ○ Summary ROC curves are approximations of the true ROC since the method used to complete the meta-analysis uses a finite number of discrete data points instead of a continuous predictor (Martinez-Camblor et al.,2017)
	
	Implications
	• Per the review authors, the sensitivity and specificity of PCT suggest inadequate diagnostic accuracy
	• PCT is not to be used in isolation to detect bacterial pneumonia in clinical practice

Funding	**Funding** • The systematic review and meta-analysis were supported by the Women & Children's Health Research Institute Resident/Fellow Trainee Research Grant and Strategy for Patient-Oriented Research Support Unit

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Tsou et al. (2020)

Design	**Diagnostic Quantitative Synthesis and Meta-analysis**
Objective(s)	To evaluate the diagnostic accuracy of procalcitonin (PCT) for childhood bacterial pneumonia

Methods	**Criteria for considering studies for this review**
	• **Types of studies:** Studies investigating the diagnostic accuracy of PCT for bacterial pneumonia
	• **Participants:** Children and adolescents ≤ 21 years of age presenting with symptoms suggestive of pneumonia
	• **Index test (new test):** Serum PCT; considered positive if above the cut-off level
	• **Reference standard (gold standard test):** Defined by results from any of the following alone or in combination (There is no gold standard test for the diagnosis of bacterial pneumonia)
	  ○ Chest x-ray
	  ○ Blood culture
	  ○ Sputum culture
	  ○ Bronchoalveolar lavage (BAL) culture
	  ○ Polymerase chain reaction (PCR) of nasopharyngeal secretions
	  ○ Antibody and/or antigen assays
	  ○ Absence of viral lower respiratory tract infection (LRTI) as diagnosed by a respiratory PCR panel and/or clinical diagnosis
	
	Search methods for identification of studies
	• **Electronic databases searched:**
	  ○ PubMed
	  ○ EMBASE
	• **Search strategy employed:**
	  ○ A uniform search strategy was developed through a consensus meeting
	  ○ Database search timeframes included the database inception through September 2019
	  ○ MeSH terms from PubMed and Emtree terms from EMBASE were combined with free text words
	  ○ The 'OR' connector was used for similar concepts
	  ○ The 'AND' connector was used to combine concepts
	  ○ The following search terms for PCT were combined using the OR connector:'aspiration pneumonia' OR 'atypical pneumonia' OR 'bacterial pneumonia' OR 'bronchial pneumonia' OR'ventilator-associated pneumonia' OR 'pneumonia' OR'acute respiratory distress syndrome' OR 'pneumonitis'.
	  ○ The search terms for children were defined as: 'children' OR 'child' OR 'newborn' OR 'infant' OR 'pediatric' OR 'adolescent.' These search results were further combined using the 'AND' connector.
	  ○ The search was limited to human studies and children below 21 years of age
	  ○ The search did not restrict publication date, language, or country.
	• **Searching other resources (such as reference list):**
	  ○ Reference lists in all known reviews and primary studies were checked manually
	
	Data collection and analysis
	• **Inclusion criteria:**
	  ○ Human studies
	  ○ Children and adolescents ≤ 21 years of age
	  ○ Symptoms suggestive of pneumonia included, but were not limited to: rales, tachypnea, dyspnea, cough, decreased breath sounds, focal wheezing, or fever
	• **Exclusion criteria:**
	  ○ Case reports

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- Case series with less than 10 cases
- Animal studies
- Publications without original data

- **Population:** Pediatric patient (≤21 years of age) presenting with symptoms suggestive of pneumonia
- **Prior testing:** Not reported
- **Setting:** Inpatient, outpatient clinic, emergency department, intensive care unit
- **Study Design:** Diagnostic systematic review/meta-analysis of 25 studies (see *Study Selection*) with subgroup analysis
  - Different cut-offs of PCT levels: Bacterial pneumonia versus nonbacterial lower respiratory tract infection (LRTI)
  - Different PCT testing systems: LUMItest and VIDAS
  - Different cut-off PCT levels: Typical bacterial pneumonia versus non-typical bacterial LRTI, nonbacterial LTRI, and atypical pneumonia
  - Age below five years
- **Data collection process:**
  - Two authors independently conducted the study selection and data extraction
  - A consensus meeting resolved discrepancies between the reviewers
  - If consensus could not be reached, a third reviewer performed as arbitrator
  - The initial evaluation was based on screening of titles and abstracts
  - Both review authors completed full-text screenings, where group consensus was used to resolve conflicts
  - Data extracted included study characteristics, study design, setting, patient characteristics, patient inclusion criteria, PCT testing system, cut-off values, outcomes, reference test, and quantitative data required to construct a standard diagnostic test 2 x 2 table.
  - For studies that reported the crude or adjusted odds ratio for the association between elevated PCT and bacterial pneumonia, the review authors extracted the data on the crude or adjusted odds ratio and 95% confidence interval
- **Assessment of the certainty of the evidence-** The review authors used the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool to assess the methodological quality of the selected studies before conducting the meta-analysis
- **Data Synthesis (what statistical plan do the authors establish a priori):**
  - **Cut offs:**
    - 0.5 ng/mL – 2.0 ng/mL
    - Optimal cut-offs were determined a priori to perform subgroup analyses based on different cut-off levels (0.5 ng/mL, 1.0 ng/mL, and 2.0 ng/mL)
  - **Sensitivity:** Pooled sensitivity was calculated with 95% confidence intervals of PCT for diagnosing bacterial pneumonia in children
  - **Specificity:** Pooled specificity was calculated with 95% confidence intervals of PCT for diagnosing bacterial pneumonia in children
  - **Heterogeneity:** The degree of between-study heterogeneity was calculated using the I^2 test
  - **ROC:**
    - A hierarchical summary receiver operating characteristic (HSROC) curve was constructed and the AUROC was calculated.
    - For studies that reported odds ratio from adjusted or unadjusted regression models, the review authors calculated the pooled odds ratio with 95% confidence intervals of association between elevated PCT and bacterial pneumonia using a random-effect model
  - **Additional analyses**: Fagan plot analyses were conducted using the presumed pre-test probabilities of pneumonia of 25%, 50%, 75%, and the corresponding positive and negative post-test probabilities of pneumonia were further calculated.
  - **Publication bias:**
    - The presence and effect of publication bias were examined using Deek's test

	○ If publication bias was present, the trim-and-fill method proposed by Duvall and Tweedie was used to reach a symmetric funnel plot and imputed summary estimate
Results	**Study Selection** **Number of articles identified:** *N* = 140 **Full-text articles assessed for eligibility:** *n* = 88 ○ **Studies included in qualitative synthesis:** *n* = 25 ▪ There were 12 prospective cohort studies, six retrospective studies, two case-control studies, and five unspecified cohort studies ▪ Three studies were conducted in the United States, 13 in Europe, five in Asia, two in South America, and two in Africa ▪ Study subjects were primarily children and adolescents under 17, with nine studies on children with a mean age less than five years. ▪ Eight studies used LUMItest PCT kit (Brahms Diagnostica, Berlin, Germany) and four studies used VIDA BRAHMS PCT immunoassay kit (bioMérieux, Marcy l'Etoile, France) ▪ As a reference test for the diagnosis of bacterial pneumonia: • Ten studies used a combination of microbiology testing and imaging (e.g., blood culture, sputum cultures, pleural effusions culture, antibody/antigen assays, nasopharyngeal PCR, chest x-ray) • Four studies used chest X-ray alone • Seven studies used antibody and/or antigen assays without blood cultures • One study used broncho-alveolar lavage culture alone (>10,000 CFU/mL) • One study used sputum culture alone • One study used blood culture alone • One study did not specify the reference standard ▪ Twelve studies compared typical bacterial pneumonia with either one or a combination of atypical pneumonia, viral pneumonia, and unknown etiology ○ **Studies included in quantitative synthesis:** *n* = 21 ▪ Studies that reported true positive (TP), false positive (FP), true negative (TN), and false negative (FN) allowing for meta-analysis of diagnostic accuracy, while six studies reported crude or adjusted OR for the association of elevated PCT with bacterial pneumonia allowing for meta-analysis of the OR and the 95% CI. **Synthesis of quality of evidence** (strength of evidence) • In general, the studies included were considered acceptable methodological quality with minimal applicability concerns in the patient population, as well as the index and reference tests. • Studies varied regarding reference standards used for diagnosis of pneumonia. • Based on the QUADAS-2 Domain (Figure 4.): ○ Flow and Timing: ~25% of the studies were considered to have a high risk of bias, and 20% were considered unclear ○ Reference Standard: 20% of studies were considered to have a high risk of bias; regarding Applicability, ~10% of studies were considered to have a high risk of bias ○ Index Test: <10% of studies were considered to have a high risk of bias ○ Patient Selection: ~10% of studies were considered to have a high risk of bias; regarding Applicability, ~15% of studies were considered to have a high risk of bias **Synthesis of quantitative evidence** • **Sensitivity:** Pooled sensitivity was 0.64 (0.53 - 0.74) ○ **0.5 ng/mL:** 0.68 (0.50 – 0.82); 11 studies

	○ **1.0 ng/mL:** 0.61 (0.43 – 0.77); 9 studies ○ **2.0 ng/mL:** 0.59 (0.40 – 0.76); 8 studies • **Specificity:** Pooled specificity was 0.72 (0.64 - 0.71) ○ **0.5 ng/mL:** 0.60 (0.47 – 0.72); 11 studies ○ **1.0 ng/mL:** 0.64 (0.54 – 0.73); 9 studies ○ **2.0 ng/mL:** 0.71 (0.58 – 0.81); 8 studies • **Heterogeneity:** Pooled I^2 = 99 (98 – 99) ○ **0.5 ng/mL:** 99 (98 – 99); 11 studies ○ **1.0 ng/mL:** 97 (95 – 99); 9 studies ○ **2.0 ng/mL:** 95 (98 – 99); 8 studies • **ROC:** Pooled ROC was 0.74 (0.70 - 0.78) ○ **0.5 ng/mL:** 0.68 (0.64 – 0.72); 11 studies ○ **1.0 ng/mL:** 0.67 (0.62 – 0.71); 9 studies ○ **2.0 ng/mL:** 0.71 (0.67 – 0.71); 8 studies • **Publication bias:** ○ Derek's funnel plot asymmetry test suggested significant publication bias ($p < 0.01$) ○ The trim-and-fill method proposed by Duvall and Tweedie was used, and eight missing studies were imputed and added to the left of the funnel plot to make it symmetric ○ The summary log-transformed diagnostic odds ratio (DOR) declined from *DOR* = 1.45, 95% CI [1.02, 1.87] to *DOR* = 0.76, 95%CI [0.28, 1.24] after the addition of the missing studies
Discussion	**Limitations** (as reported by review authors) • Reference tests varied across studies. The heterogeneous reference standards with varied sensitivities and specificities across diagnostic modalities were a concern for misclassification bias. • Studies used various PCT testing systems • Various pathogens causing bacterial pneumonia in different age groups introduced heterogeneity, resulting in difficulty interpreting results • Inability to determine when in the course of illness PCT was tested in individual studies **Implications** • The systematic review/meta-analysis suggested there is moderate diagnostic accuracy of PCT for the diagnosis of bacterial pneumonia in children • Review authors suggest findings provide evidence that PCT should not be used alone to diagnose bacterial pneumonia, though proposed it could be used in conjunction with other factors that contribute to the diagnosis, including clinical presentation, and laboratory and imaging findings • Review authors found there was no optimal cut-off of PCT to accurately differentiate between bacterial and viral pneumonia • Review authors stratified for PCT testing systems and found diagnostic accuracy remained suboptimal
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Evidence Based Practice

Critically Appraised Topic (CAT): Procalcitonin in Bacterial Pneumonia

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