2-2024

Procalcitonin in Sepsis and Bacterial Infection

Children's Mercy Kansas City

Critically Appraised Topic (CAT): Procalcitonin in Sepsis and Bacterial Infection

Specific Care Question

In pediatric patients with suspected sepsis, what is the diagnostic accuracy of procalcitonin predicting clinically or microbiologically confirmed serious or invasive bacterial illness?

Rationale for Question Asked

The diagnostic accuracy of procalcitonin (PCT) in pediatric patients with possible sepsis to predict serious or invasive bacterial infection is an important inquiry due to the need for reliable and timely identification of sepsis in this vulnerable population. Assessing the diagnostic accuracy of PCT tests in this context helps clinicians with risk stratification, guiding effective clinical decisions for patients with suspected sepsis. As PCT tests become more readily available, a review of the literature is necessary to inform efficacious ordering and interpretation in patients with suspected sepsis and bacteremia.

The comparison of PCT to C-reactive protein is beyond the scope of this review. Please review the AAP Febrile Infant Clinical Practice Guideline for recommendations.

Overview and Certainty of Evidence

In infants aged 2 days to 36 months, the overall positive predictive value (PPV) ranged from 8.1% to 50.4% for invasive bacterial infection (IBI) and serious bacterial infection (SBI) at cutoffs of 0.5 and 2.0. The PPV indicates positive results should be interpreted with caution, as there is a significant chance of false positives. The negative predictive value (NPV) ranged from 88.5% to 99.6% for IBI and SBI at cutoffs of 0.5 and 2.0. The NPV indicates negative results are relatively reliable.

For toddlers and children (1.5 years -19 years) the PPV among ranged from 10% to 29% at cutoffs of 0.5 and 2.0. The PPV indicates positive results should be interpreted with caution, as there is a significant chance of false positives. The NPV ranged from 94% to 98% at cutoffs of 0.5 and 2.0, indicating negative results are relatively reliable.

Infants age 2 days to 36 months

In a systematic review (*N* = 7,260) by Trippella et al. (2017), the authors observed a high diagnostic accuracy for PCT in detecting IBI in infants 2 days to 36 months with fever without an apparent source (see Table 1). PCT showed 82% sensitivity to rule out IBI at a cutoff of 0.5 ng/mL and 94% specificity to rule in IBI at a cutoff of 2 ng/mL. In detecting SBI, PCT diagnostic accuracy was moderate, with 55% sensitivity at a cutoff of 0.5 ng/mL and a 95% specificity at 2 ng/mL. Because of the higher sensitivity and specificity with IBI, the authors speculated that PCT may perform better in the diagnosis of the most severe infections, such as bacterial meningitis, bacteremia, and sepsis. Overall, the positive predictive value (PPV) ranged from 8.1% to 50.4% for IBI and SBI at cutoffs of 0.5 and 2.0. The negative predictive value (NPV) ranged from 88.5% to 99.6% for IBI and SBI at cutoffs of 0.5 and 2.0.

The Receiver Operating Characteristic (ROC) was 0.9164, indicating a high level of diagnostic accuracy for PCT at a cutoff of 0.5 ng/mL in detecting IBI.
The ROC was 0.9666, indicating a high level of diagnostic accuracy for PCT at a cutoff of 2 ng/mL in detecting IBI.
The ROC was 0.7950, indicating a moderate level of diagnostic accuracy for PCT at a cutoff of 0.5 ng/mL in detecting SBI.
The ROC was 0.8842, indicating a moderate level of diagnostic accuracy for PCT at a cutoff of 2 ng/mL in detecting SBI.

Certainty Of The Evidence For Trippella et al. (2017) Certainty of evidence is based on what was reported by the authors of the meta-analysis. The authors reported the risk of bias of patient selection domain was considered high in three of the 13 studies due to inappropriate exclusions. The risk of bias of reference standard domain was considered unclear in six of the 13 studies due to not reporting whether the reference standard results were interpreted without knowledge of the results of the index test. The risk of bias in the flow and timing domain was considered high in six of the 13 studies because the reference standard was not applied to all patients (i.e., blood cultures were not performed in the entire study population). For applicability concerns, the

reference standard domain for seven of the 13 studies were labeled as high risk due to the reference standard for diagnosis of SBI or IBI (i.e., the diagnosis of bacterial pneumonia was based on the result of a chest x-ray, not a culture exam on biological samples)

Toddlers and Older Children (Range 1.5 -19 years)

Three studies (Byler et al., 2021; Nellis et al., 2016; Waterfield et al., 2020) reported on the diagnostic accuracy of procalcitonin in children with sepsis, bacterial infection, and systemic inflammatory response syndrome (see Table 1). The median age across all the studies (*N* = 1,564) ranged from 2.7 to 13 years. At a cutoff of 0.5 ng/mL (*n* = 357), two of the studies (Nellis et al., 2016; Waterfield et al., 2020) reported a sensitivity range of 77%-88.5%, specificity range of 40%-48.5%, PPV range of 10%-21%, and NPV range of 94-97%. At a cutoff of 2 ng/mL (*n* = 357), two studies (Nellis et al., 2016; Waterfield et al., 2020) reported sensitivity range of 64%-69%, specificity range of 74-92%, PPV range of 20-29%, and NPV range of 94%-97%.

Byler et al. (2021) reported on diagnostic accuracy of procalcitonin in children with systemic inflammatory response syndrome (*N* = 1,207). Cutoffs were determined based on the desired sensitivity and specificity of 90%. At 90% specificity for severe sepsis, cutoff values were 2.72 ng/mL. At 90% sensitivity, the cutoff value was within the lab range for normal PCT levels.

The Area Under the Curve (AUC) across all studies ranged from 0.621 to 0.783, indicating a poor to moderate level of accuracy for the PCT at detecting sepsis and bacterial infection.
The PPV among all studies ranged from 10% to 29% across all cutoffs. The PPV indicates positive results should be interpreted with caution, as there is a significant chance of false positives.
The NPV among all studies ranged from 94% to 98% across all cutoffs, indicating negative results are relatively reliable.

Certainty Of The Evidence Overall certainty of the evidence was considered very low due to risk of bias, indirectness, and inconsistency. Risk of bias was determined to be serious due to the differing reference standards used across the five studies. Additionally, there was serious indirectness due to the inclusion of patients from non-western countries, in which the presence of other diseases and variations of prevalence could affect diagnostic accuracy. Additionally, there is serious inconsistency due to the heterogeneity of the different diagnoses and ages of patients.

Table 1
Included Studies

AUTHOR (year)	Country	Study Children (N) Age (range)	Inclusion Criteria	Gold standard	Prevalence	Cut off	Sensitivity	Specificity	ROC/AUC	PPV / NPV	Positive LR / Negative LR
Age 2 days to 36 months											
Trippella et al. (2017)	Western countries	N = 7260	2 days to 36 months with fever without apparent source, evaluated in hospital	Microbiologically confirmed (MC) or clinical criteria (CC)	1-46%	0.5 ng/mL 2 ng/mL	0.5 ng/mL IBI: 0.82, 95% CI [0.73, 0.90] 2 ng/mL IBI: 0.61,	0.5 ng/mL IBI: 0.86, 95% CI [0.85, 0.87]	0.5 ng/mL IBI: ROC 0.9164	**PPV** 0.5 ng/mL IBI: 8.1% 2 ng/mL IBI: 14.7%	**Positive LR** 0.5 ng/mL in IBI: 4.78 2 ng/mL in IBI: 10.5

		2 days to 36 months	or ambulatory settings in Western countries; SBI and/or IBI, a priori defined. UTI, Bacterial Gastroenteritis, Bacterial Pneumonia, Cellulitis				95% CI [0.49, 0.73] 0.5 ng/mL SBI: 0.55, 95% CI [0.52, 0.58] 2 ng/mL SBI: 0.30, 95% CI [0.27, 0.34]	2 ng/mL IBI: 0.94, 95% CI [0.93, 0.95] 0.5 ng/mL SBI: 0.85, 95% CI [0.84, 0.86] 2 ng/mL SBI: 0.95, 95% CI [0.94, 0.95]	2 ng/mL IBI: ROC 0.9666 0.5 ng/mL SBI: ROC 0.7950 2 ng/mL SBI: ROC 0.8842	0.5 ng/mL SBI: 41% 2 ng/mL SBI: 50.4% **NPV** 0.5 ng/mL IBI: 99.6% 2 ng/mL IBI: 99.3% 0.5 ng/mL SBI: 90.8% 2 ng/mL SBI: 88.6%	0.5 ng/mL in SBI: 3.6 2 ng/mL in SBI: 5.8 **Negative LR** 0.5 ng/mL in IBI: 0.2 2 ng/mL in IBI: 0.4 0.5 ng/mL in SBI: 0.5 2 ng/mL in SBI: 0.74
Toddlers and Older Children (Range 1.5 -19 years)											
Nellis et al. (2016)	USA	N = 144 Age in years (IQR) 2.7 (0.9-11.7)	<21 years with fever admitted to intensive care	MC	13.2% (*n* = 27) for positive blood cultures	PCT 0.5 ng/mL PCT 2 ng/mL	**Cutoff 0.5 ng/mL** 88.5% **Cutoff 2 ng/mL** 69.2%	**Cutoff 0.5 ng/mL** 48.7% **Cutoff 2 ng/mL** 74.4%	AUC 0.783	**Cutoff 0.5ng/mL** PPV 21% NPV 97% **Cutoff 2ng/mL** PPV 29% NPV 94%	**Cutoff 0.5ng/mL** Positive LR 1.7 Negative LR 0.97 **Cutoff 2ng/mL** Positive LR 2.7 Negative LR 0.4168
Waterfield et al. (2020)	UK	N = 213 < 18 years median age was 2 years, 9 months	<18 years with serious Bacterial Infection (features of meningococcal infection, sepsis, or meningitis with blood available for PCT testing)	MC or CC	4.7% (n = 10)	PCT 0.5 ng/mL PCT 2 ng/mL	**Cutoff 0.5 ng/mL** 70% [35, 92] **Cutoff 2 ng/mL** 64% [58, 72]	**Cutoff 0.5 ng/mL** 40% [14, 73] **Cutoff 2 ng/mL** 92% [87, 95]	AUC 0.7	**Cutoff 0.5ng/mL** PPV 10% NPV 98% **Cutoff 2ng/mL** PPV 20% NPV 97%	**Cutoff 0.5ng/mL** Positive LR 2.02 Negative LR 0.46 **Cutoff 2ng/mL** Positive LR 4.83 Negative LR 0.65
Byler et al. (2021)	USA	N = 1207 Age: <18 years Median age (IQR) Serve Sepsis 6 (0,19.7) No Severe	Patients for whom an automatic sepsis alert was triggered	SIRS criteria	8.2% (n = 100) Criteria for Severe sepsis 3.4% (*n* = 41) for positive blood culture	90% sensitivity = 0.08 ng/mL 90% specificity = 2.72 ng/mL	**Cutoff 0.08ng/mL** 90%	**Cutoff 2.72 ng/mL** 90%	AUC 0.621 95% CI [0.517, 0.725]		

		Sepsis 13 (3.2, 22.9)									

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

Children's Mercy KANSAS CITY
Evidence Based Practice

Critically Appraised Topic (CAT): Procalcitonin in Sepsis and Bacterial Infection

#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* = 580

Question Originator
J. Herigon, MD, MPH
Medical Librarian Responsible for the Search Strategy
K. Swaggart, MLIS, AHIP
EBP Team Responsible for Analyzing the Literature
K. Hess, PharmD
M. Gripka, MT (ASCP) SM
A. Melanson, OTD, OTR/L
K. Ott, OTD, OTR/L
EBP Medical Director Responsible for Reviewing the Literature
K. Berg, MD, FAAP
EBP Team Member Responsible for Reviewing, Synthesizing, and Developing this Document
J. Dusin, MS, RD, LD, CPHQ

Date Developed: February 2024

If you have questions regarding this CAT – please contact evidencebasedpractice@cmh.edu

Children's Mercy KANSAS CITY
Evidence Based Practice

Critically Appraised Topic (CAT): Procalcitonin in Sepsis and Bacterial Infection

Trippella et al., 2017

Design	**Diagnostic Quantitative Synthesis and Meta-analysis**
Objective(s)	To evaluate the diagnostic accuracy of procalcitonin (PCT) in detecting serious or invasive bacterial infection (SBI or IBI) in children with fever without apparent sources through a literature review and provide pooled estimates for sensitivity and specificity when considering differing cutoff values.

Methods	**Criteria for considering studies for this review**
	• **Types of studies:**
	  ○ Observational cohort studies
	• **Participants:** Children ≤ 18 years of age
	• **Index test (new test):** PCT
	• **Reference standard (gold standard test):** Culture exam on biological samples
	• **Target Condition(s):**
	  ○ SBI
	  ○ IBI
	
	Search methods for identification of studies
	• **Electronic databases searched:**
	  ○ MEDLINE database
	  ○ PubMed was used as the search engine
	• **Search strategy employed:**
	  ○ July 31, 2007 – July 31, 2017 (10-year)
	  ○ Search terms were limited to title or abstract
	  ○ MeSH terms used were procalcitonin *AND* (fever *OR* feverish *OR* febrile) *AND* (children *OR* child *OR* infants)
	  ○ Articles evaluating the diagnostic value of PCT to detect SBI/IBI in children with fever without an apparent source
	• **Searching other resources (such as reference list):**
	  ○ The references of relevant articles were further crosschecked
	
	Data collection and analysis
	• **Inclusion criteria:**
	  ○ English language
	  ○ Patient population was represented by children ≤ 18 years with fever without an apparent source
	  ○ Children evaluated in the hospital or ambulatory settings in Western counties
	  ○ Serum concentrations of PCT were obtained as part of the first patient evaluation, and the results were reported quantitatively
	  ○ SBI and/or IBI was defined a priori
	• **Exclusion criteria:**
	  ○ Studies enrolling patients with comorbidities (e.g., immune deficiency, major congenital malformation, chronic disease, neoplasia)
	  ○ Studies conducted on adult populations (> 18 years of age)
	  ○ Studies not conducted in Western countries
	  ○ Reviews, case reports, comments
	  ○ Studies with insufficient data about PCT diagnostic performance (inability to calculate sensitivity and/or specificity)
	• **Population:** Children ≤ 18 years of age presenting with fever without an apparent source
	• **Prior testing:** Studies identifying serum concentrations of PCT were obtained as part of the first patient evaluation were included in the review.
	• **Setting:** Hospital or ambulatory settings in Western countries
	• **Study Design:** Meta-analysis of four retrospective and nine prospective cohort studies
	• **Data collection process:**
	  ○ Two investigators independently reviewed the searches and evaluated every article

Date Developed: February 2024

If you have questions regarding this CAT – please contact evidencebasedpractice@cmh.edu

	○ Extracted information from the eligible studies included: publication year, country of origin, characteristics of population sample, outcome measured, reference standard, and diagnostic performances of PCT testing ○ SBI and IBI were considered measured outcomes ▪ SBI was used to indicate a broad spectrum of conditions (e.g., bacterial meningitis, sepsis, bacteremia, urinary tract infections, pneumonia, bacterial gastroenteritis, bone or soft tissue infections) ▪ IBI indicated the subgroup of most severe infections (e.g., bacterial meningitis, sepsis, and bacteremia) ○ The number of children with true-positive (TP), false-positive (FP), false-negative (FN), or true-negative (TN) test results, for all the available cutoff values were extracted from each study ○ Analyses were performed using Meta-Disc version 1.4 for all analyses other than the analyses for potential publication bias. • **Assessment of the certainty of the evidence:** QUADAS-2 tool was used to assess the quality, applicability, and risk of bias of the included studies • **Data Synthesis (what statistical plan do the authors establish a priori):** ○ The joint distribution of true-positive rate (TPR) and false-positive rate (FPR) was analyzed with a summary receiver operating characteristic (SROC) curve, using the area under the curve (AUC) as an overall summary measure of the curve's behavior. ○ Four meta-analyses were performed and pooled estimates for sensitivity, specificity, and diagnostic odds ratio for PCT at the cutoffs 0.5 and 2 ng/mL were calculated considering first IBI, then SBI. ○ A sub-analysis included studies reporting data only for children under 3 months of age. ○ Data were pooled using the Der Simonian and Laird method ○ An additional analysis was performed, excluding studies one at a time (leave-one-study-out-cross-validations), looking for variations in inconsistency and pooled estimates for sensitivity and specificity • **Cutoffs:** Cutoffs of 0.5 and 2 ng/mL were calculated considering first IBI, then SBI • **Sensitivity:** Four meta-analyses were performed and pooled estimates for sensitivity at the cutoffs of 0.5 and 2 ng/mL were calculated considering first IBI, then SBI. • **Specificity:** Four meta-analyses were performed and pooled estimates for specificity at the cutoffs of 0.5 and 2 ng/mL were calculated considering first IBI, then SBI. • **Heterogeneity:** ○ The random-effects model was used to account for heterogeneity between studies. ○ The magnitude of heterogeneity between studies was expressed as the variance percentage attributable to between-studies heterogeneity (I^2). ▪ I^2 values < 25% were considered to represent low inconsistency ▪ I^2 values between 25% and 75% were considered to represent moderate inconsistency ▪ I^2 values > 75% were considered to represent high inconsistency ○ Meta-regression was performed to investigate potential sources of heterogeneity • **ROC:** The joint distribution of TPR and FPR was analyzed with a SROC curve, using the AUC as an overall summary measure of the curve's behavior. ○ Values of AUC between 0.50 and 0.70 were considered to represent low accuracy ○ Values of AUC between 0.70 and 0.90 were considered to represent moderate accuracy ○ Values > 0.90 were considered to represent high accuracy • **Publication bias:** Potential publication bias was assessed using Begg's funnel plot, in which asymmetry suggests possible publication bias, and Egger's regression test. Publication bias was determined using STATA software.
Results	**Study Selection**

Number of articles identified: *N* = 130
Full-text articles assessed for eligibility: *n* = 19
- **Studies included in qualitative synthesis:** *n* = 13
- **Studies included in quantitative synthesis:** *n* = 12
  - Overall 7,260 children
  - All studies were conducted in an emergency department, with an SBI/IBI prevalence ranging between 1.0% and 45.9%.
  - Each study analyzed one or more cutoff values, ranging from 0.12 to 2.0 ng/mL.
  - The most frequently considered cutoff values were 0.5 ng/mL and 2ng/mL.

Synthesis of quality of evidence (strength of evidence): *n* = 13
- Risk of Bias:
  - The patient selection domain was considered high risk in three of the studies due to inappropriate exclusions by the study authors
  - The index test domain was considered low risk in all 13 studies
  - The reference standard domain was considered unclear risk in six of the studies as the authors did not report whether the reference standard results were interpreted with or without knowledge of the results of the index test.
  - The flow and timing domain was considered high risk in six of the studies as the reference standard was not applied to all the patients (e.g., blood cultures were not performed in the entire study population)
- Concern on Applicability:
  - The patient selection domain was considered low risk in all 13 studies
  - The index test domain was considered low risk in all 13 studies
  - The reference standard domain was considered high risk in seven studies as the reference standard for the diagnosis of SBI or IBI was not a culture of biological samples (e.g., the diagnosis of bacterial pneumonia was based on results on a chest x-ray)
- One study with more than two 'high risks' was judged to be of low quality; therefore, the study was excluded from the analysis.

Synthesis of quantitative evidence: *n* = 12
- **Sensitivity:** Ranged between 0.20 and 1.00 when considering all cutoff values
  - Diagnostic accuracy of PCT at a cutoff of **0.5 ng/mL** in detecting **IBI** [five studies]: *DOR* = 0.82, 95% CI [0.73, 0.90]
  - Diagnostic accuracy of PCT at a cutoff of **2 ng/mL** in detecting **IBI** [four studies]: *DOR* = 0.61, 95% CI [0.49, 0.73]
  - Diagnostic accuracy of PCT at a cutoff of **0.5 ng/mL** in detecting **SBI** [seven studies]: *DOR* = 0.55, 95% CI [0.52, 0.58]
  - Diagnostic accuracy of PCT at a cutoff of **2 ng/mL** in detecting **SBI** [four studies]: *DOR* = 0.30, 95% CI [0.27, 0.34]
  - Diagnostic accuracy of PCT in children **under 3 months of age** in detecting **IBI** with a cutoff of **0.5 ng/mL** [four studies]: *DOR* = 0.81, 95% CI [0.70, 0.90]
  - Diagnostic accuracy of PCT in children **under 3 months of age** in detecting **IBI** with a cutoff of **2 ng/mL** [four studies]: *DOR* = 0.62, 95% CI [0.48, 0.75]
  - Diagnostic accuracy of PCT in children **under 3 months of age** in detecting **SBI** with a cutoff of **0.5 ng/mL** [four studies]: *DOR* = 0.48, 95% CI [0.44, 0.53]
  - Diagnostic accuracy of PCT in children **under 3 months of age** in detecting **SBI** with a cutoff of **2 ng/mL** [four studies]: *DOR* = 0.25, 95% CI [0.21, 0.30]

- **Specificity:** Ranged between 0.25 and 0.97 when considering all cutoff values

- Diagnostic accuracy of PCT at a cutoff of **0.5 ng/mL** in detecting **IBI** [five studies]: *DOR* = 0.86, 95% CI [0.85, 0.87]
- Diagnostic accuracy of PCT at a cutoff of **2 ng/mL** in detecting **IBI** [four studies]: *DOR* = 0.94, 95% CI [0.93, 0.95]
- Diagnostic accuracy of PCT at a cutoff of **0.5 ng/mL** in detecting **SBI** [seven studies]: *DOR* = 0.85, 95% CI [0.84, 0.86]
- Diagnostic accuracy of PCT at a cutoff of **2 ng/mL** in detecting **SBI** [four studies]: *DOR* = 0.95, 95% CI [0.94, 0.95]
- Diagnostic accuracy of PCT in children **under 3 months of age** in detecting **IBI** with a cutoff of **0.5 ng/mL** [four studies]: *DOR* = 0.86, 95% CI [0.85, 0.87]
- Diagnostic accuracy of PCT in children **under 3 months of age** in detecting **IBI** with a cutoff of **2 ng/mL** [four studies]: *DOR* = 0.94, 95% CI [0.93, 0.95]
- Diagnostic accuracy of PCT in children **under 3 months of age** in detecting **SBI** with a cutoff of **0.5 ng/mL** [four studies]; *DOR* = 0.87, 95% CI [0.86, 0.89]
- Diagnostic accuracy of PCT in children **under 3 months of age** in detecting **SBI** with a cutoff of **2 ng/mL** [four studies]: *DOR* = 0.95, 95% CI [0.94, 0.96]

- **Heterogeneity:**
  - Diagnostic accuracy of PCT at a cutoff of **0.5 ng/mL** in detecting **IBI** [five studies]: 0.0% for sensitivity and 82.1% for specificity
  - Diagnostic accuracy of PCT at a cutoff of **2 ng/mL** in detecting **IBI** [four studies]: 0.0% for both sensitivity and specificity
  - Diagnostic accuracy of PCT at a cutoff of **0.5 ng/mL** in detecting **SBI** [seven studies]: 89.6% for sensitivity and 94.8% for specificity
  - Diagnostic accuracy of PCT at a cutoff of **2 ng/mL** in detecting **SBI** [four studies]: 89.9% for sensitivity and 82.2% for specificity
  - Diagnostic accuracy of PCT in children **under 3 months** of age in detecting **IBI** with a cutoff of **0.5 ng/mL** [four studies]: Not reported
  - Diagnostic accuracy of PCT in children **under 3 months** of age in detecting **IBI** with a cutoff of **2 ng/mL** [four studies]: Not reported

- **ROC:**
  - Diagnostic accuracy of PCT at a cutoff of **0.5 ng/mL** in detecting **IBI**: AUC was 0.9164 (standard error [SE] = 0.0225) with Q^* = 0.8493 (SE = 0.0255)
  - Diagnostic accuracy of PCT at a cutoff of **2 ng/mL** in detecting **IBI**: AUC was 0.9666 (SE = 0.0403) with Q^* = 0.9144 (SE = 0.0627)
  - Diagnostic accuracy of PCT at a cutoff of **0.5 ng/mL** in detecting **SBI**: AUC was 0.7950 (SE = 0.0377) with Q^* = 0.7315 (SE = 0.0328)
  - Diagnostic accuracy of PCT at a cutoff of **2 ng/mL** in detecting **SBI**: AUC was 0.8842 (SE = 0.1335) with Q^* = 0.8147 (SE = 0.1364)
  - Diagnostic accuracy of PCT in children **under 3 months** of age in detecting **IBI** with a cutoff of **0.5 ng/mL** [four studies]: Not reported
  - Diagnostic accuracy of PCT in children **under 3 months** of age in detecting **IBI** with a cutoff of **2 ng/mL** [four studies]: Not reported
  - Symmetric SROC: AUC was 0.8784 (SE = 0.0148) with Q^* = 0.8088 (SE = 0.0149)

- **Publication bias:**
  - The funnel plots generated from the studies considering IBI appeared symmetric, while studies considering SBI generated asymmetric funnel plots.
  - The Begg's rank correlation test (p-values ranged from 0.462 – 0.764) and the Egger's linear regression test (*p*-values ranged from 0.170 – 0.341) indicated no evidence of publication bias among studies

Discussion	**Limitations** • The meta-analysis included a small number of studies. • Selection bias in systematic reviews and meta-analyses may arise from the search methodology. • Failure to recover all data during the literature search process is a concern. • MEDLINE was the only database searched, therefore relevant publications from other databases may have been missed. • The literature review only included studies published in English. • Studies completed outside of Western countries were excluded, potentially overlooking topics regarding the role of PCT in other infections. • High heterogeneity level between studies. **Implications** • Further analysis with high-quality data and evidence from multicenter studies is warranted to confirm findings. • The management of children with fever without apparent source is challenging. • Biomarkers constitute a helpful tool when clinical assessment is challenging. • The usefulness of PCT in clinical practice continues to be debatable.
Funding	**Funding** • The authors received no funding for writing the manuscript and have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Date Developed: February 2024

If you have questions regarding this CAT – please contact evidencebasedpractice@cmh.edu

References

Baraka, A., & Zakaria, M. (2018). Presepsin as a diagnostic marker of bacterial infections in febrile neutropenic pediatric patients with hematological malignancies. *International Journal of Hematology*, *108*, 184-191.

Byler, S., Baker, A., Freiman, E., Herigon, J. C., & Eisenberg, M. A. (2021). Utility of specific laboratory biomarkers to predict severe sepsis in pediatric patients with SIRS. *The American Journal of Emergency Medicine*, *50*, 778-783.

Kaiserova, E., & Kolenova, A. (2016). The role of CRP, PCT, IL-6 and presepsin in early diagnosis of bacterial infectious complications in paediatric haemato-oncological patients. *Neoplasma*, *63*(5).

Nellis, M. E., Pon, S., Giambrone, A. E., Coleman, N. E., Reiss, J., Mauer, E., & Greenwald, B. M. (2016). The diagnostic accuracy of serum procalcitonin for bacteremia in critically ill children. *Infectious diseases in clinical practice (Baltimore, Md.)*, *24*(6), 343.

Trippella, G., Galli, L., De Martino, M., Lisi, C., & Chiappini, E. (2017). Procalcitonin performance in detecting serious and invasive bacterial infections in children with fever without apparent source: a systematic review and meta-analysis. *Expert review of anti-infective therapy*, *15*(11), 1041-1057.

Waterfield, T., Maney, J.-A., Lyttle, M. D., McKenna, J. P., Roland, D., Corr, M., Patenall, B., Shields, M. D., Woolfall, K., & Fairley, D. (2020). Diagnostic test accuracy of point-of-care procalcitonin to diagnose serious bacterial infections in children. *BMC pediatrics*, *20*, 1-6.

Yoon, S. H., Kim, E. H., Kim, H. Y., & Ahn, J. G. (2019). Presepsin as a diagnostic marker of sepsis in children and adolescents: a systemic review and meta-analysis. *BMC Infectious Diseases*, *19*, 1-11.

Date Developed: February 2024

If you have questions regarding this CAT – please contact evidencebasedpractice@cmh.edu