Procalcitonin as a Prognostic Indicator of Risk for Sepsis in the Neonate

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Abstract

Introduction. Procalcitonin (PCT) is a biomarker that rises at the onset of bacterial infection while remaining relatively low in other inflammatory processes. Diagnosing serious bacterial infection (SBI) in neonates presenting with fever without a source (FWS) is challenging and utilizing PCT can improve this process. This paper presents a synthesis of the evidence supporting PCT as a prognostic indicator in neonates. **Methodology.** A comprehensive literature review was conducted to develop practice recommendations. A guideline, the Intermountain Healthcare Care Process Model (2013), was modified to include PCT, which was then validated by a panel of clinical experts. **Results.** Evidence supports the use of PCT as a prognostic indicator. Clinical expert feedback supports using the modified Intermountain Healthcare Care Process Model (2013) in practice. **Discussion.** PCT is a valuable serum biomarker that should be examined in the workup of neonates presenting with FWS and a modified algorithm to include PCT is presented.

Background and Significance

According to the Sepsis Alliance Organization (2014), approximately 44,000 children per year develop sepsis, resulting in 4,400 deaths and sepsis is the third leading cause of death for the entire U.S. population. Sepsis is one of the most costly diseases to treat in the U.S., totaling more than $20 billion in 2011 (Agency for Healthcare Research and Quality [AHRQ], 2013). In the neonatal population, an estimated one to two incidents of sepsis occur for every 1,000 births, and for every 100 sepsis workups, about one is found to be positive (Payne, 2004). With the high cost of sepsis to patients, families, and society, early detection of SBI is essential, especially in neonates as SBI can rapidly lead to sepsis with few specific clinical signs.

Sepsis in the neonate is categorized as either early onset sepsis (EOS) or late onset sepsis (LOS). EOS is sepsis occurring in the first 72 hours of life and is usually associated with the acquisition of maternal microorganisms. LOS is sepsis occurring after 72 hours of age and is usually associated with microorganisms from the environment. The early clinical signs of SBI in the neonate are nonspecific and include leukocytosis, tachycardia, and fever among others. When more specific signs are exhibited, such as hypotension, thrombocytopenia, or increased lactate levels, the patient has often already progressed to multiple organ dysfunction, and it is usually too late for life-saving measures (Wacker, Prkno, Brunkhorts, & Schlattmann, 2013). In a study of over 3,000 neonates only 58% of those with bacterial meningitis or bacteremia appeared clinically ill (Pantell et al., 2004). This lack of early specific signs of SBI may trigger providers to prescribe unnecessary antibiotics in neonates with FWS. Additionally, the concern of antibiotic overuse resulting in drug-resistant organisms may cause providers to delay treatment until a bacterial organism is more favorably suspected; if SBI is, in fact, present, such a delay can rapidly lead to shock. Further, evidence suggests antibiotic overuse has a high correlation with

the development of lifelong irritable bowel disease (IBD) in children (Kronman, Zaoutis,

Haynes, Feng, & Coffin, 2012) and is associated with newly diagnosed juvenile idiopathic

arthritis (Horton et al., 2015). With the dangers inherent in delay of treatment as well as in the

unnecessary use of antibiotics, prognostic indicators for the presence of SBI are essential. A

neonate is usually hospitalized until cultures are negative (about 72 hours), and average daily

costs associated with hospital stays per infant surpass $3,500 in the neonatal intensive care unit

(Muraskas & Parsi, 2008).

Certain serum biomarkers such as acute phase reactants and complete blood count (CBC)

with differential are commonly used to assess for the presence of a bacterial infection. A

commonly used acute phase reactant is C-reactive protein (CRP), a protein that is released by the

liver during inflammatory processes such as infection and atherosclerotic disease. Erythrocyte

sedimentation rate (ESR) is another acute phase reactant that is not as sensitive as CRP; CRP

rises faster in an inflammatory process and falls faster during recovery (Anderson & Schmidt,

2010). Newer research indicates that another biomarker, procalcitonin, may be correlated with a

bacterial infection as well.

Procalcitonin (PCT) rises in the early phase of bacterial infectious processes while

remaining low in viral and other inflammatory responses. PCT is mainly secreted by the liver

and is a prohormone of calcitonin (England, Del Vecchio, & Aronoff, 2014). PCT was first

discussed as being immunoreactive in 1983, but its exact mechanism was unclear (Hatzistilianou,

2010). There is now evidence that inflammation, specifically cytokine release during a microbial

infection, may cause an upregulation of the gene expression responsible for the release of PCT

from various tissues throughout the body (Hatzistilianou, 2010). Increased levels of the cytokines

interleukin (IL)- 1β, tumor necrosis factor (TNF)-α, and IL-6 have been associated with bacterial

infections, and are thought to induce rapid release of PCT from tissues throughout the body (Hatzistilianou, 2010; Schuetz et al., 2013; Stannard, 2014). Inversely, PCT release appears to be inhibited by interferon γ, which has been noted to elevate with viral infections (Schuetz et al., 2013; Stannard, 2014). PCT rises within 4 hours and peaks within 6 hours of bacterial infection (Mann, Wood, & Wade, 2011). CRP and white blood cell (WBC) count rise quickly but are not as specific for SBI. CRP takes 14-48 hours to change significantly after onset of infection and peaks around 18 to 72 hours of disease onset (Nasir, Mele, Babayo, & Yahaya, 2015), and though it is often higher in bacterial infections, it rises in response to most inflammatory processes such as trauma, viral, bacterial, or fungal infection, autoimmune disorders, and myocardial infarction (Pagana & Pagana, 2010). WBC levels are also nonspecific and rise in all of the aforementioned processes in addition to states such as emotional stress (Pagana & Pagana, 2010). Although CRP is more sensitive than ESR and WBC, there remains no single marker specific enough to guide clinicians on its own. With the limitations of the currently used serum biomarkers, adding the utilization of PCT levels to the workup has the potential to improve diagnostic accuracy leading to a significant improvement in patient outcomes.

In healthy subjects, serum PCT levels are below 0.05 ng/mL. However, the PCT concentration with bacterial sepsis is usually much greater than 1-2 ng/mL and can increase exponentially with the degree of infection. Levels of up to 1000 ng/mL have been seen with severe bacterial sepsis. PCT levels may be elevated in viral infections, chronic inflammatory disorders, or autoimmune processes but are still generally <0.25 ng/mL (Thermo Scientific, 2013). PCT has also been found to be higher and more variable in the first three days of life (Bohnhorst et al., 2012; Shah & Padbury, 2014). With the commonly used assays, PCT results can be produced within 18 to 26 minutes (Lloyd & Kuyl, 2012; Thermo Scientific, 2013). PCT

has been included in several European protocols for the management of febrile children, but its value is not completely defined (Gomez et al., 2012). PCT is not consistently used as a biomarker in late onset sepsis (LOS) despite its potential as a more sensitive early biomarker for SBI (Gomez et al., 2012; Stein, Schachter-Davidov, Babai, Tasher, & Somekh, 2015).

According to the *Health Care Blue Book* (2014), the fair market price for CRP and CBC with differential are approximately $34.00 and $20.00 respectively, while the PCT test is more costly at $69.00. However, with the potential prevention of sepsis, reduction of antibiotic use, and reduced hospital stays, the higher cost of PCT is outweighed by the benefits to patients.

As aforementioned, there is a high morbidity and mortality of neonatal SBI and sepsis due to their immature immune systems and immature blood brain barrier. Additionally, clinicians face great difficulty in diagnosing SBI and sepsis in the neonate due to lack of early clinical signs. Due to these difficulties, the utilization of a potentially effective biomarker such as procalcitonin should be evaluated.

Clinical Question

In neonatal patients (3-90 days of age) presenting with FWS, is PCT an effective biomarker as part of the neonatal sepsis workup?

Search Methods

Key words related to the clinical question were selected for a review of the literature. The first search was conducted in EBSCO (Elton Bryson Stephens Company) Host for peer-reviewed articles published since 2012 using the search terms "procalcitonin" and "neonate"; 30 articles populated. To meet criteria, the population had to be term neonates with concern for late-onset sepsis; therefore, articles focusing on preterm infants or early-onset sepsis were excluded. Nine articles met criteria; one article was not available in English and was excluded. The remaining

eight articles were included for review. An evaluation table of the final studies is presented in Appendix A.

To ensure all related articles were found, the same search was conducted, this time with the terms "procalcitonin" and "newborn", which populated 31 articles. From the 31 articles, 26 articles were duplicates, and five did not meet inclusion criteria.

PubMed was searched next using the key title terms "procalcitonin", "neonate", and "sepsis" for articles published since 2012, which populated zero articles. The search term "sepsis" was eliminated, and the search was repeated yielding five articles. Four of the articles were duplicates from the prior search on EBSCO Host, and the remaining article focused on fungal infections and was thus excluded.

Finally, references were hand-searched for additional articles directly related to the clinical question published since 2012 that did not populate in previous literature searches. Dima et al. (2012) referenced an article published in 2012 titled *"Diagnostic value of procalcitonin in well-appearing young febrile infants",* which was retained for review. Other article titles were either not relevant or were published before the year of 2012.

Evaluation of Data

All articles, which included five studies, three literature reviews, and one systematic review, found PCT to be useful in identifying bacterial infection and provided evidence to support its use in the workup of a neonate presenting with FWS. Auriti et al. (2012) performed an observation study, which included 557 normal birth weight neonates, and concluded that a PCT value ≤2.4 ng/mL carried a very low risk of sepsis in normal birth weight infants and recommended PCT be utilized in the septic workup of a neonate. In a prospective study of 58 proven cases of LOS, Bohnhorst et al. (2012) concluded that PCT should be included in the

workup of a febrile neonate and that adding a PCT level with the cut-off value at >0.7 ng/mL to

the workup increases sensitivity to nearly 100%. Bohnhorst et al. (2012) recommended this

conservative cut-off value to prevent missing any neonatal sepsis cases. Dima et al. (2012)

published a literature review concluding that PCT is more sensitive and specific for detection of

neonatal sepsis than CRP and ESR and should be added to the workup of a neonate with FWS. In

a retrospective study of 1,112 well appearing neonates presenting with FWS Gomez et al. (2012)

found that PCT was the most sensitive marker of ruling in and ruling out invasive bacterial

infection, being superior to CRP and WBC. Gomez et al. (2012) recommended a PCT cut-off

value of 2 ng/mL. Nasir et al. (2015), performed a systematic review of PCT in the management

of neonatal sepsis and found that using PCT guided treatment yielded better outcomes than any

other biomarker and should be used in conjunction with other tests (e.g. CBC, WBC, CRP) when

caring for a neonate with possible sepsis. Nasir et al. (2015) made no formal PCT cut-off value

recommendation, but they did show PCT values as low as 0.6 ng/mL in sepsis.

        Another literature review by Shah and Padbury (2014), discussed the use of PCT in

neonatal sepsis as promising and recommended further studies to better understand its diagnostic

value. The authors did define PCT as a better indicator of neonatal sepsis than CRP and

recommended its use in conjunction with other biomarkers in the workup of a neonate with

possible sepsis (Shah & Padbury, 2013). Stein et al. (2015) studied the differences between CRP,

PCT, and the recently discovered soluble triggering receptor expressed on myeloid cells (s-

TREM-1) and found that no single biomarker is adequate to use alone, and no formal

recommendations were provided. However, Stein et al. (2015) included neonates with many

symptoms other than fever, such as fussiness, apathy, or rash, which may limit the significance

of their results.

The literature review by Stemberger and Tešović (2012) of the Pediatric Infectious Disease Department at the University Hospital for Infectious Diseases in Croatia also stress the importance of utilizing PCT in the workup of a septic neonate. Sugitharini, Prema, and Thangam (2013) studied the utilization of different biomarkers, including CRP and PCT, and found that multiple biomarkers should be used in detecting neonatal sepsis. Evidence appraised in this literature review supports recommending the use of PCT as a valuable biomarker in the workup of sepsis in the neonatal population.

Conceptual Frameworks

The Academic Center for Evidence-Based Practice (ACE) Star Model of Knowledge Transformation was chosen as the conceptual framework to guide this project. The ACE Star was developed to improve the quality of care through the transformation of knowledge to nursing practice (Schaffer, Sandau, & Diedrick, 2013). The assumptions of knowledge transformation are that knowledge transformation is derived from multiple sources; knowledge from research, experience, authority, trial and error and theoretical principles is transformed through steps including application, integration, and evaluation. The five points of knowledge transformation depicted in the ACE Star Model "move research-based discovery from one point to the next in translating evidence into guidelines for practice," (McEwen & Wills, 2014). Evidence from the literature review was synthesized and transformed into clinical recommendations for practice; the recommendations are then integrated into practice through individual and organizational efforts. (Schaffer et al., 2013).

Sample and Approach

A panel of clinical experts was recruited via non-random sampling, convenience sampling, and snowball sampling techniques (Kim & Mallory, 2014). Since the sampling

methods chosen were based on feasibility, an effort was focused on obtaining a sample of

providers from different regions of the U.S. to convene a heterogeneous sample of practitioners

and avoid a decrease in statistical power (see Appendix D). A goal of eight experts was chosen

for the sample size as this is a manageable size to analyze and display the discussion question

results. Representations from two disciplines practicing in four regions of the U.S. were recruited

to identify variations in practice (Polit and Beck, 2014).

Participants were informed that the questionnaire was voluntary and identity protected.

The sample consisted of pediatric clinical expert providers caring for neonates with FWS. An

expert provider was defined as a pediatric provider who had a minimum of seven years

experience. Only experts currently in practice were recruited for the sample. Demographic data

of the experts included discipline (e.g. MD, DO, NP), specialty credentials (e.g. PNP, NNP,

Pediatrician, Neonatologist), the number of years in practice, practice setting (PICU, Pediatrics),

practice location (e.g. urban or rural), and geographic region of practice. Personal information

was protected including names, phone numbers, e-mail addresses, and titles that may reveal

identity, and providers were informed that such sensitive information would not be included in

the paper.

Data Collection

Data collection to determine the validity of the revised care process model was

accomplished by developing and distributing the 8-item dichotomous questionnaire with an

optional 1-item dichotomous question and an optional 2-item discussion question set completed

by clinical experts (see Appendix C). The mixture of dichotomous and discussion questions

resulted in both qualitative and quantitative data.

The modified care process model and questionnaire, along with an introductory paragraph and summation of the evidence, was either hand-delivered or e-mailed to the participants. Participants were given four weeks to complete and return the questionnaire. An emailed or verbal reminder was given to the participants at the end of the second week if no response was received. The Intermountain Healthcare Care Process Model (2013) modified to include PCT is the independent variable, and the content validity will predict consistency in the management of care, to include appropriate utilization of tests and antibiotic use, and to decrease morbidity and mortality from sepsis, which are the dependent variables.

Data Analysis

Evaluation of data was performed using descriptive statistics, one of the most common ways to analyze and group ordinal data (Kim & Mallory, 2014). Frequencies and percentages were also utilized to describe what the data from the questionnaire show. A description of how many of the experts report that they would use, recommend, and believe the Intermountain Healthcare Care Process Model (2013) modified to include PCT is consistent with current standards of care for the neonate presenting with FWS was reported. There were no comparisons of different groups before or after intervention, and so inferential statistics was not utilized (Terry, 2012).

<div align="center">**Results**</div>

Expert providers consisted of four pediatric intensivists, two pediatric hospitalists, and two pediatric intensive care nurse practitioners, from different geographic regions (see Appendix D). Of the expert providers, four had >20 years experience, two had between 16 and 20 years experience, and two had 8-15 years of experience (see Appendix D). One of the providers was also the medical director of a pediatric and pediatric intensive care unit in a Southwest

community hospital. Another provider was the director of a pediatric acute care and neonatal

nurse practitioner program at a highly ranked Ivy League university and was also past president

of the Association of Faculties of Pediatric Nurse Practitioners. Another provider was a pediatric

intensive care nurse practitioner that also practiced as the manager of a nurse practitioner group

at a Southwest children's hospital. Data from the results show 100% of the providers believe the

modified Intermountain Healthcare Care Process Model (2013) is consistent with current

standards for care of a neonate presenting with FWS, serves as an effective discriminator for

LOS or SBI recognition in the well-appearing neonate presenting with FWS, is comprehensive,

that there are no unnecessary or missing items, would use this modified care process model in

practice, and would recommend this modified care process model to other providers. However,

one participant did not find the modified care process model easy to follow for use in daily

practice as it seemed to take some time to understand how to read the algorithm. Another

provider answered that the modified care process model should include the sensitivity and

specificity of PCT. In the discussion question set, another provider wrote that he would

recommend utilizing different antibiotic regimens than those published by Intermountain

Healthcare (2013). Another provider included in the discussion question set that he would like to

see more research on percentages of chances for different conditions such as septic arthritis and

more research on specificity and sensitivity of PCT in general. Only one of the eight providers

answered that PCT was included in a protocol for the workup of neonates presenting with FWS

in their practice.

Conclusion

Though only one provider answered that PCT was included in a protocol for the workup

of neonates presenting with FWS in their practice, current data show the importance of utilizing

PCT in the septic workup of the neonate, and formal recommendations are warranted. With early identification of SBI, outcomes associated with neonatal sepsis will improve due to decreased morbidity, unnecessary antibiotic therapy, and decreased hospital length of stays. Evidence synthesized from the literature supports PCT as an additional test offering greater specificity as an indicator for late onset sepsis in the neonate. The Intermountain Healthcare Care Process Model (2013) was modified to include PCT with criteria based on this current evidence. The validity of the clinical practice recommendations via the data analysis of the questionnaire completed by clinical experts preliminarily validate the use of this modified care process model in caring for the neonate presenting with FWS. Following these guidelines will increase consistency in the management of care of a neonate presenting with FWS, to include appropriate utilization of tests and antibiotic use, and decrease morbidity and mortality from sepsis.

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Appendix A

Evaluation Table

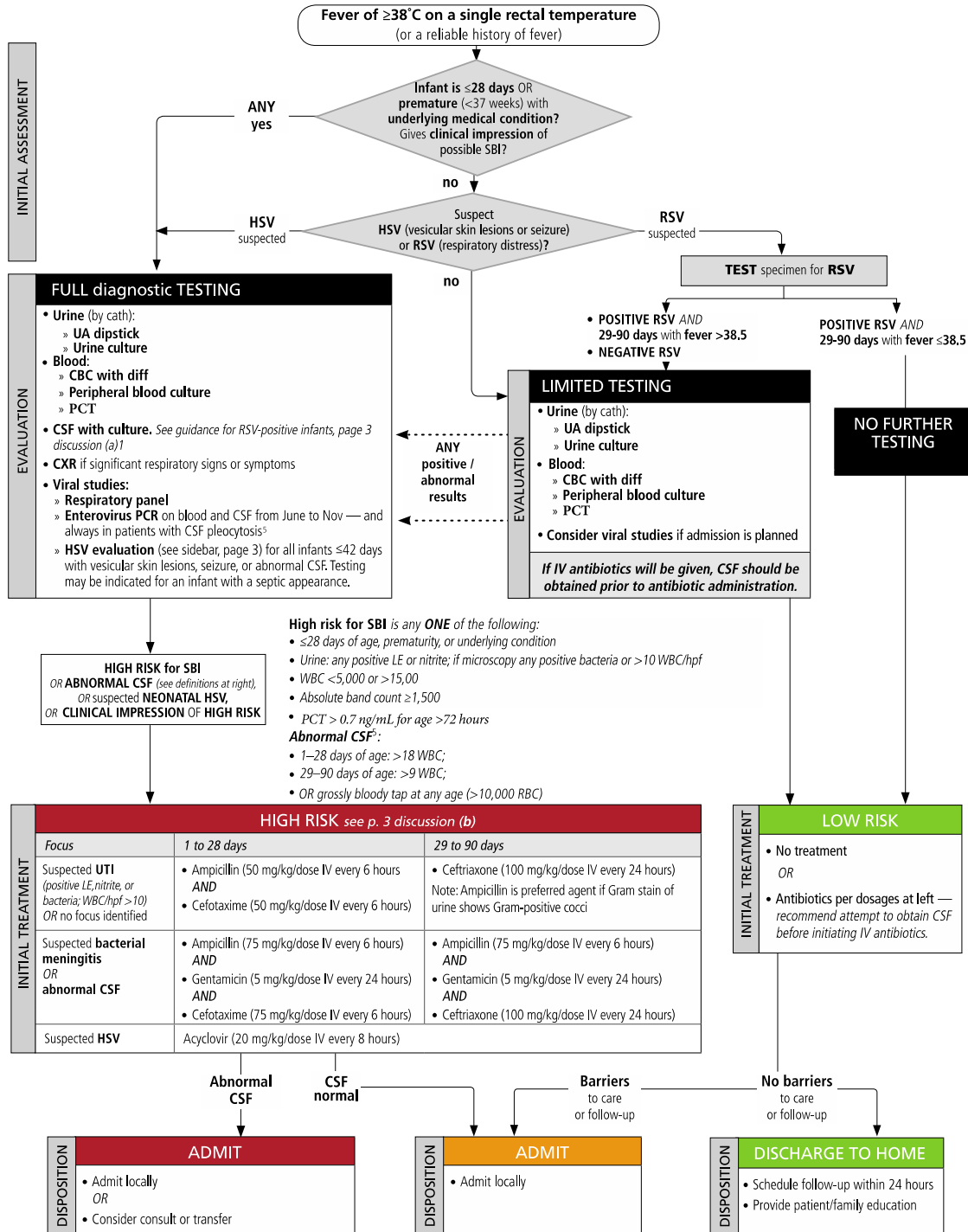| Author	Year	Study Design	Sample Size	Recommend PCT	PCT > WBC and/or CRP	WBC and/or CRP > PCT	Cut-off Value Recommendations
1	2012	OS	557	X			PCT ≤2.4 ng/mL++
2	2012	PS	58	X	X		0.7 ng/mL*
3	2012	LR		X	X		
4	2012	RS	1,112	X	X		2 ng/mL++
5	2015	SR		X	X		
6	2013	LR	3,244	X	X		
7	2015	PS	112				
8	2012	LR		X		X	
9	2013	OS	179	X			

++low risk of sepsis, * increased sensitivity to nearly 100%

CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; IL-6, Interleukin-6;
LR, Literature review; N/A, Not applicable; OS, Observational study; PCT, Procalcitonin; PS,
Prospective study; RS, Retrospective study; SR, Systematic review; WBC, White blood cell.

Appendix B

WORKUP OF THE WELL-APPEARING FEBRILE NEONATE (3-90 DAYS OF AGE)

INITIAL ASSESSMENT

Fever of ≥38°C on a single rectal temperature
(or a reliable history of fever)

Infant is ≤28 days OR **premature** (<37 weeks) with **underlying medical condition?** Gives **clinical impression** of possible SBI?

ANY yes →

no

Suspect **HSV** (vesicular skin lesions or seizure) or **RSV** (respiratory distress)?

HSV suspected →

RSV suspected →

TEST specimen for **RSV**

no

EVALUATION

FULL diagnostic TESTING

- **Urine** (by cath):
  - » UA dipstick
  - » Urine culture
- **Blood:**
  - » CBC with diff
  - » Peripheral blood culture
  - » PCT
- **CSF with culture.** *See guidance for RSV-positive infants, page 3 discussion (a)1*
- **CXR** if significant respiratory signs or symptoms
- **Viral studies:**
  - » Respiratory panel
  - » **Enterovirus PCR** on blood and CSF from June to Nov — and always in patients with CSF pleocytosis[5]
  - » **HSV evaluation** (see sidebar, page 3) for all infants ≤42 days with vesicular skin lesions, seizure, or abnormal CSF. Testing may be indicated for an infant with a septic appearance.

ANY positive / abnormal results

- **POSITIVE RSV** *AND* **29-90 days** with **fever >38.5**
- **NEGATIVE RSV**

POSITIVE RSV *AND* **29-90 days** with **fever ≤38.5**

LIMITED TESTING

- **Urine** (by cath):
  - » UA dipstick
  - » Urine culture
- **Blood:**
  - » CBC with diff
  - » Peripheral blood culture
  - » PCT
- **Consider viral studies** if admission is planned

If IV antibiotics will be given, CSF should be obtained prior to antibiotic administration.

NO FURTHER TESTING

HIGH RISK for SBI
OR **ABNORMAL CSF** *(see definitions at right),*
OR suspected **NEONATAL HSV,**
OR **CLINICAL IMPRESSION** OF **HIGH RISK**

High risk for SBI *is any* **ONE** *of the following:*
- *≤28 days of age, prematurity, or underlying condition*
- *Urine: any positive LE or nitrite; if microscopy any positive bacteria or >10 WBC/hpf*
- *WBC <5,000 or >15,00*
- *Absolute band count ≥1,500*
- *PCT > 0.7 ng/mL for age >72 hours*

Abnormal CSF[5]:
- *1–28 days of age: >18 WBC;*
- *29–90 days of age: >9 WBC;*
- *OR grossly bloody tap at any age (>10,000 RBC)*

INITIAL TREATMENT

HIGH RISK *see p. 3 discussion (b)*		
Focus	**1 to 28 days**	**29 to 90 days**
Suspected **UTI** *(positive LE, nitrite, or bacteria; WBC/hpf >10) OR* no focus identified	• Ampicillin (50 mg/kg/dose IV every 6 hours) *AND* • Cefotaxime (50 mg/kg/dose IV every 6 hours)	• Ceftriaxone (100 mg/kg/dose IV every 24 hours) Note: Ampicillin is preferred agent if Gram stain of urine shows Gram-positive cocci
Suspected **bacterial meningitis** *OR* **abnormal CSF**	• Ampicillin (75 mg/kg/dose IV every 6 hours) *AND* • Gentamicin (5 mg/kg/dose IV every 24 hours) *AND* • Cefotaxime (75 mg/kg/dose IV every 6 hours)	• Ampicillin (75 mg/kg/dose IV every 6 hours) *AND* • Gentamicin (5 mg/kg/dose IV every 24 hours) *AND* • Ceftriaxone (100 mg/kg/dose IV every 24 hours)
Suspected **HSV**	Acyclovir (20 mg/kg/dose IV every 8 hours)	

LOW RISK

- **No treatment**
  OR
- **Antibiotics** per dosages at left — *recommend attempt to obtain CSF before initiating IV antibiotics.*

Abnormal CSF

CSF normal

Barriers to care or follow-up

No barriers to care or follow-up

DISPOSITION

ADMIT
- Admit locally
  OR
- Consider consult or transfer

ADMIT
- Admit locally

DISCHARGE TO HOME
- Schedule follow-up within 24 hours
- Provide patient/family education

Appendix C

Questionnaire and Script

Hello, my name is Tara Cecil, and I am a Doctor of Nursing Practice Student at Northern Arizona University. My doctoral project is to synthesize current evidence to develop recommendations for procalcitonin (PCT) and modification of a protocol that includes criteria for PCT and other laboratory tests in caring for neonates with fever without a source. The goal is to obtain expert critical review of a protocol for PCT using an 8-item dichotomous questionnaire pertaining to clinical recommendations and protocol for PCT. This survey is voluntary. Demographics will be collected to describe participant background but no identifiable information will reported in the paper.

Content Validly Question Set:

1) Does this protocol meet the current standards of care for the neonate presenting with FWS?

A) Yes   B) No

2) Does this protocol serve as an effective discriminator for late-onset sepsis or SBI recognition

in the well-appearing neonate presenting with FWS?

A) Yes   B) No

3) Is this protocol comprehensive?

A) Yes   B) No

4) Are there any missing, critical items that should be added to this algorithm?

A) Yes   B) No

5) Are there any unnecessary items that should be deleted from this algorithm?

A) Yes   B) No

6) Is this protocol is easy to follow for use in practice?

      A) Yes   B) No

7) Would you use this protocol?

      A) Yes   B) No

8) Would you recommend this protocol to other providers?

      A) Yes   B) No

Discussion Question Set:

Responses represent provider opinions and perceptions that will contribute to implications for practice, barriers to implementation, and implications for future studies.

1) Is PCT included in a protocol for neonates presenting with FWS in your practice?

      A) Yes   B) No

2) If you answered "yes" to question 4, what are/is the missing, critical item(s) that should be

      added to this algorithm?

3) If you answered "yes" to question 5, what are/is the unnecessary item(s) that should be deleted

      from this algorithm?

Appendix D

Experience of Clinical Experts Evaluating Protocol
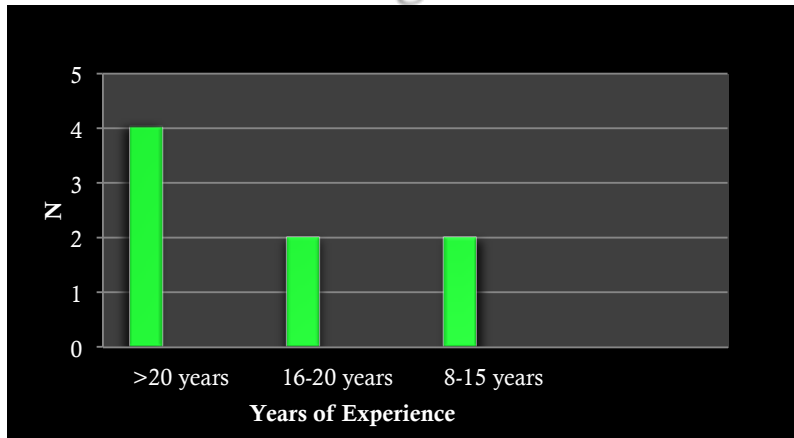
Expert providers consisted of 4 pediatric intensivists, 2 pediatric hospitalists, and 2 pediatric intensive care nurse practitioners

Demographic Location of Expert Providers

Appendix E

Results of Expert Review

	Meets current standard of care	Effective discriminator	Comprehensive	No missing items	No unnecessary items	Easy to follow	Would use	Would recommend
Experts' years of experience								
>20 years	100%	100%	100%	100%	100%	90%+	100%	100%
16-20 years	100%	100%	100%	100%	100%	100%	100%	100%
8-15 years	100%	100%	100%	90%*	100%	100%	100%	100%
*feedback indicated one provider would like sensitivity & specificity of PCT in the algorithm **+ provider mis-read first line of algorithm**								