Value of Acute Phase Reactants in the Diagnosis of Pediatric Infections

Rosemarie Santana-Arciaga, M.D., MSc.
Fellow, Philippine Pediatric Society, Inc.
Fellow, Pediatric Infectious Disease Society of the Philippines
Fellow, Philippine Society for Microbiology and Infectious Diseases

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Objective

To evaluate the utility of acute phase reactants (ESR, CRP, procalcitonin) in the diagnosis of pediatric infections.

Strategy:

Systematic Review / Meta-analysis
Evidence-based Review
Landmark Articles

Acute Phase Reactants

Heterogenous group of plasma proteins that increase or decrease in response to inflammatory stimuli such as infections, trauma, acute arthritis, systemic autoimmune disorders and neoplams.

Acute Phase Reactants

ESR and CRP: most commonly used

Procalcitonin: increasing evidence to support its usefulness as a marker in bacterial infections

Acute Phase Reactants:

TRADITIONAL USES:

- Markers of inflammation
- Measure of sickness index

Potential Wider Roles:

- Early diagnosis
- Infectious vs noninfectious
- Prognostic marker
- Antibiotic guidance strategy

- More judicious antibiotic prescriptions

Long-term Favorable Impact on:

- Antibiotic Stewardship
- Antibiotic Resistance

OUTLINE OF DISCUSSION

- **Overview of Acute Phase Reactants**
- **Acute Phase Reactants as …….**
  - Guide to ID Diagnosis
  - Guide to Antibiotic Use
- **Implications for Practice**
- **Implications for Research**

Erythrocyte Sedimentation Rate

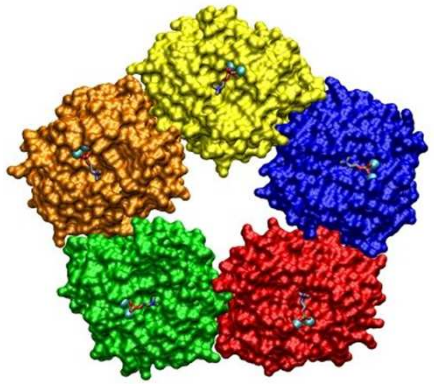
- Measures the distance that a vertical column of anticoagulated blood has fallen in one hour.
- Value in diagnosis of infection remains unclear.
- Any condition that affects RBC or fibrinogen alters the value of ESR.

- Rises within 24–48 hours.
- Falls back slowly with resolution

C-REACTIVE PROTEIN

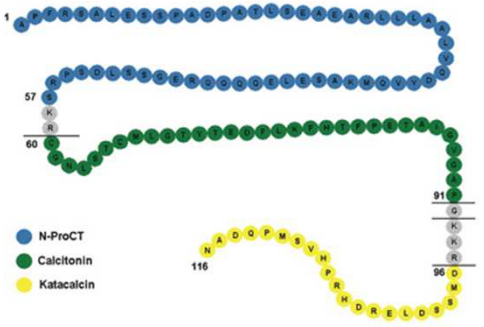
- Better measure of an acute-phase response
- More sensitive to subtle changes in the acute-phase response
- Produced by the liver in response to cytokines, mainly IL-6.
- Normal CRP level: < 10 mg/L.

- Rises after 12–24hours
- Peaks within 2–3days



PROCALCITONIN

- Peptide prehormone of calcitonin
- Normal serum concentration: <0.05 ng/ml
- Bacterial infections: PCT is stimulated by cytokines IL-1, IL-6, and TNF α
- Viral infections: PCT is downgraded by γ-interferon
- Detectable: 3–4 hours
- Peak: 6–24 hours



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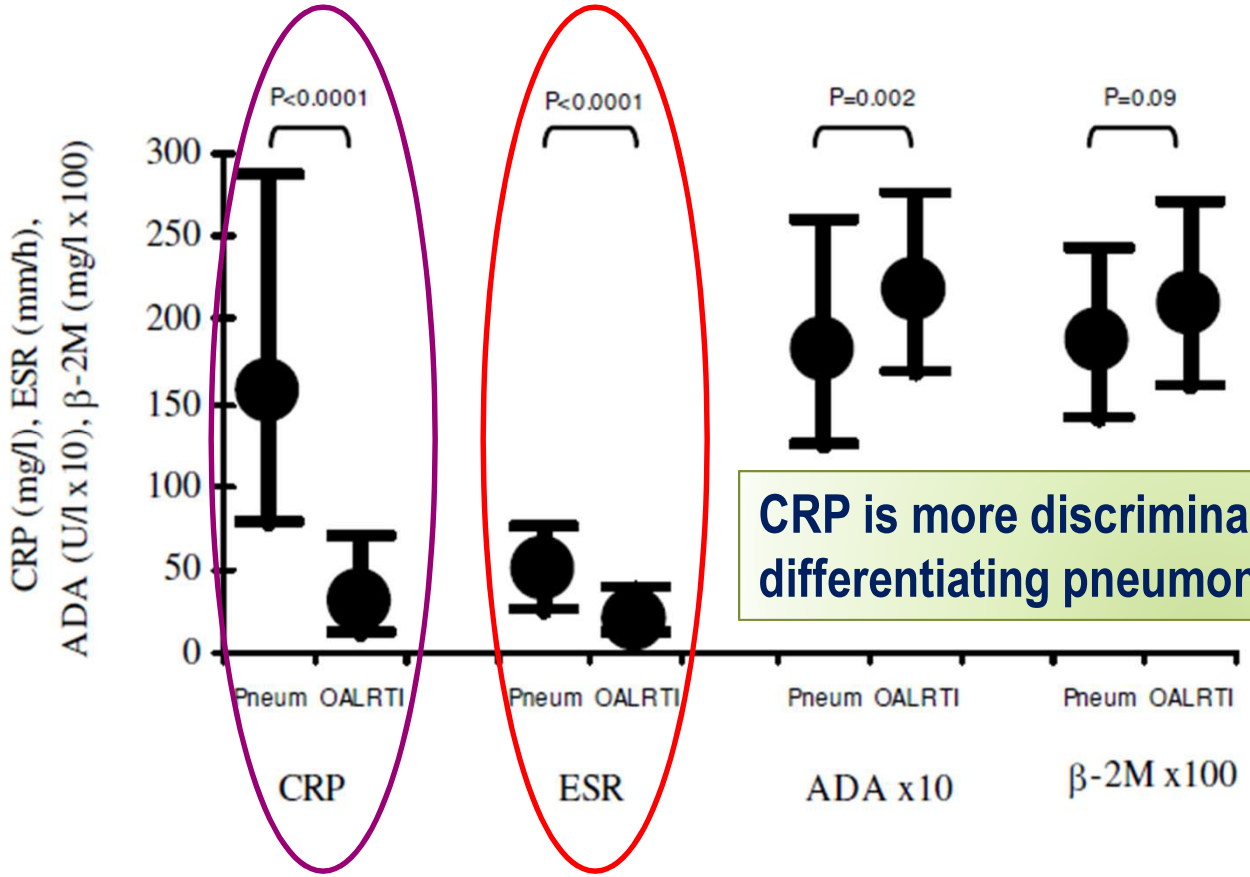
Utility of the ESR: Key Considerations

- Simple and inexpensive test of chronic inflammatory activity.
- Limited by its low sensitivity and specificity.
- ESR >100 mm/hr: infection, malignancy or temporal arteritis.
- Little value in the diagnosis of osteomyelitis, but when elevated, it can be of clinical significance to monitor response to therapy.

Unkila-Kallio L. et al: Serum CRP, ESR and WBC in acute hematogenous osteomyelitis of children. Pediatrics 1994; 1:59-62 35.
Perry M: ESR and CRP in the assessment of suspected bone infections are they reliable indices? J R Coll Surg Edinb 1996; 41:116- 118

Median and IQR of Biomarkers in Patients with pneumonic and non-pneumonic LRTI

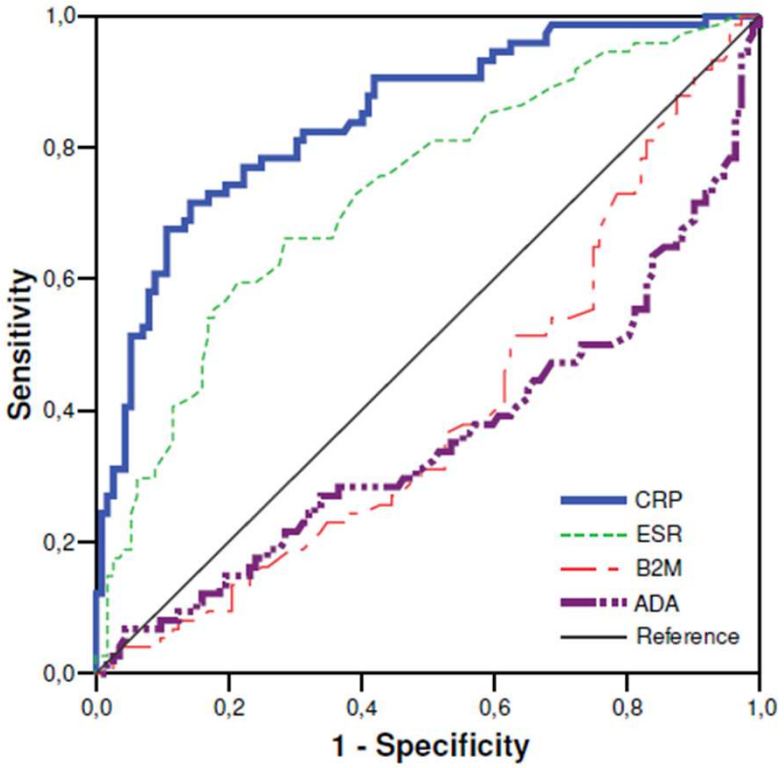


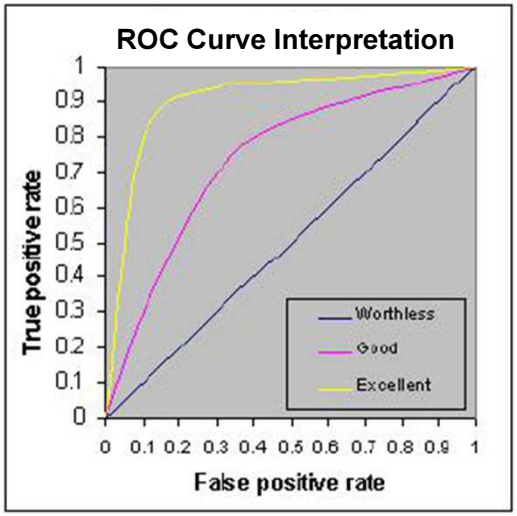
CRP is more discriminant than ESR in differentiating pneumonia and other ALRTI.

Collazos et.al Evaluation of Acute-phase Reactants, Immunologic Markers and other Clinical and Laboratory Parameters in Patients with Pneumonia and Non-pneumonic Lower Respiratory Tract Infections. *Am. J. Infect. Dis.*, 3 (1): 42-50, 2007

ROC Curve of CRP, ESR and other Immunologic Markers

Pneumonia vs Other ALRTI



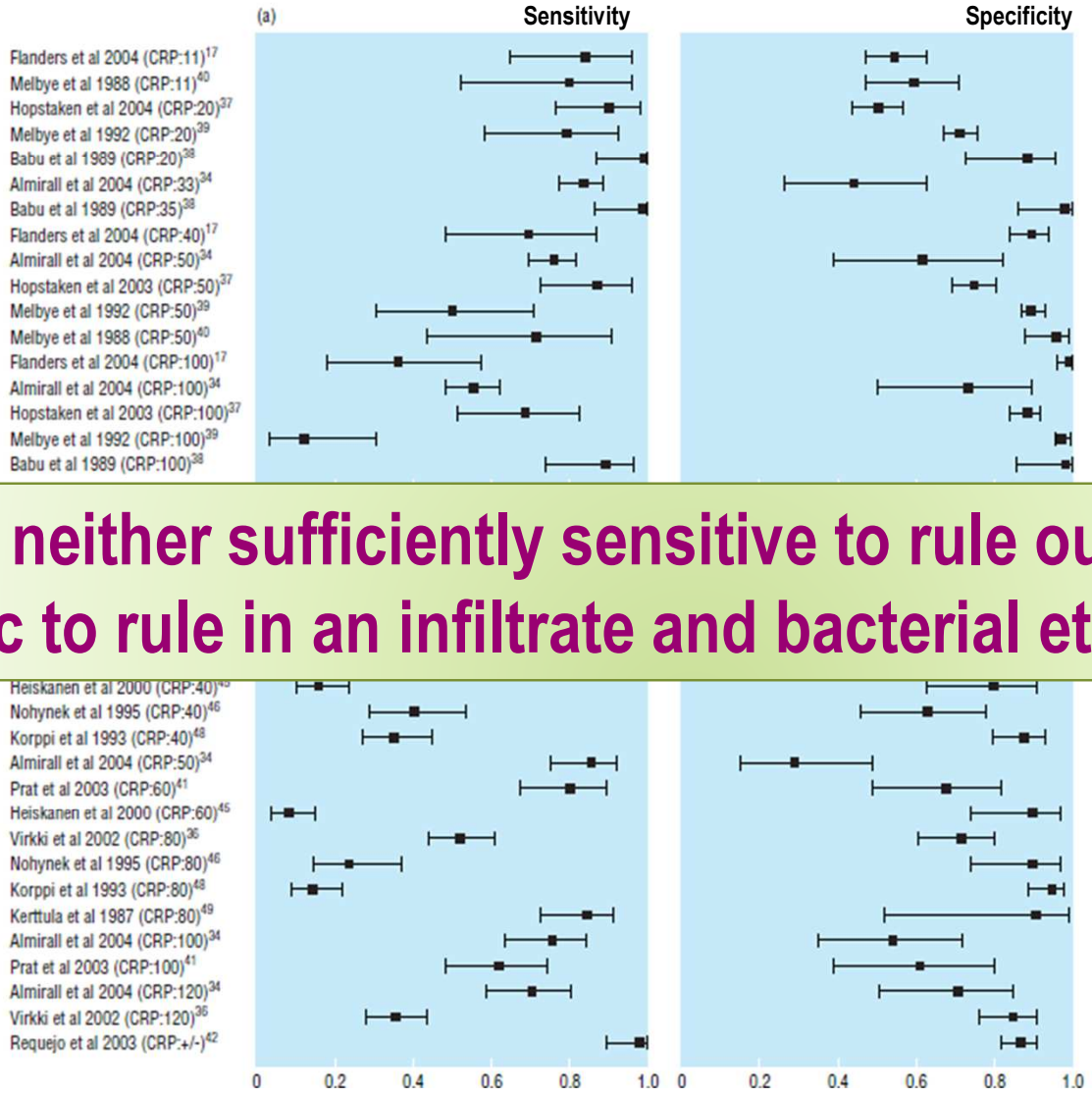


CRP: AUC = 0.93 (95% CI 0.89-0.96, p<0.0001).

CRP is a useful adjunct in differentiating pneumonia from OALRTI.

Collazos et.al Evaluation of Acute-phase Reactants, Immunologic Markers and other Clinical and Laboratory Parameters in Patients with Pneumonia and Non-pneumonic Lower Respiratory Tract Infections. *Am. J. Infect. Dis.*, 3 (1): 42-50, 2007

Sensitivity-Specificity Plot of C-Reactive Protein



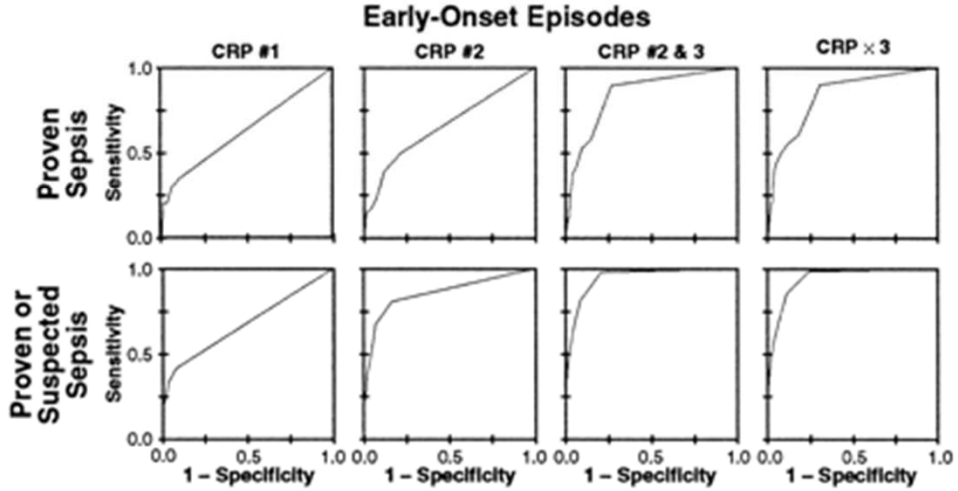
Detection of an infiltrate on CXR

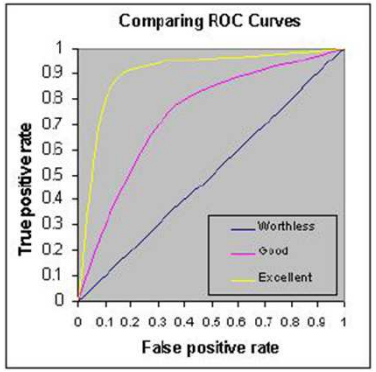
CRP is neither sufficiently sensitive to rule out nor sufficiently specific to rule in an infiltrate and bacterial etiology of LRTI.

Detection of a bacterial etiology

Van den Meer et.al. Diagnostic Value of CRP in Infections of the Respiratory Tract: Systematic Review. *BMJ*. 24 June 2005

ROC Curve for CRP in Neonatal Sepsis





- Accuracy is low during the early phase of infection.
- A normal initial CRP is not sufficient to justify withholding antibiotics.
- Serial determinations 24 to 48 hours after the onset of symptoms improves diagnostic accuracy.

Benits W et al. Serial Serum C-Reactive Protein Levels in the Diagnosis of Neonatal Infection. *Pediatrics* Oct 1998, 102:Issue4

CRP in the Diagnosis of Neonatal Sepsis

- A growing body of evidence suggests a link between gestational age and CRP kinetics with lower CRP values and lower CRP response to infection in preterm compared to term newborns.

Hofer N. Neonatology 2012;102:25–36

- CRP undergoes a physiologic 3-day-rise after birth
- Non-infectious confounders: meconium aspiration syndrome.

Resch B. "Neonatal Bacterial Infection" April 30, 2013

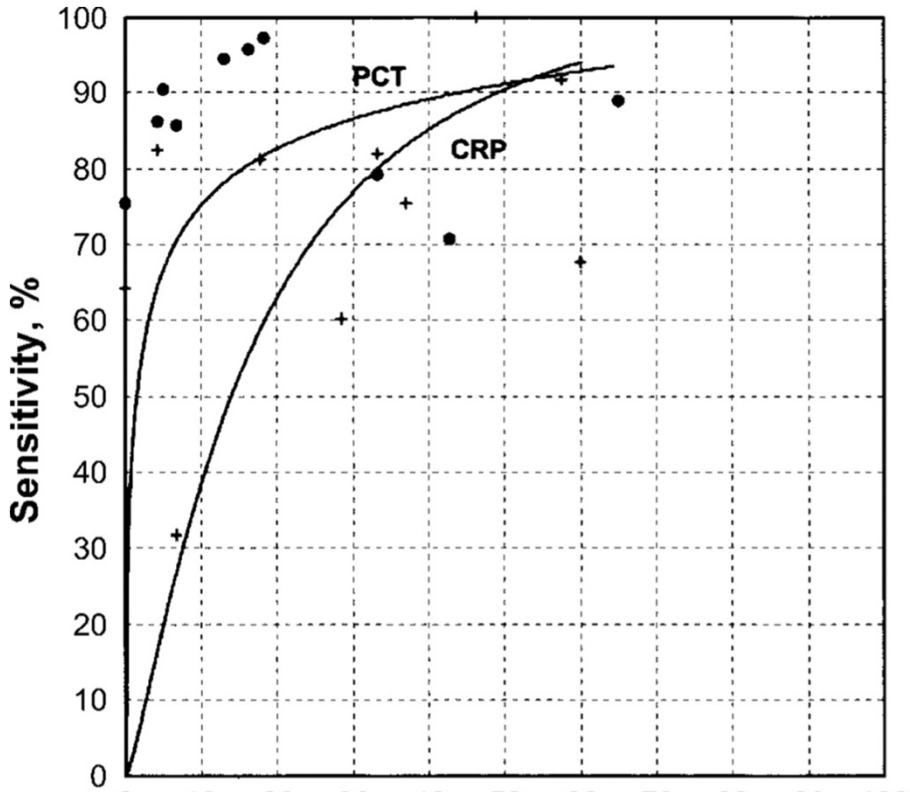
Procalcitonin and CRP as markers for bacterial infections vs noninfective causes of inflammation.

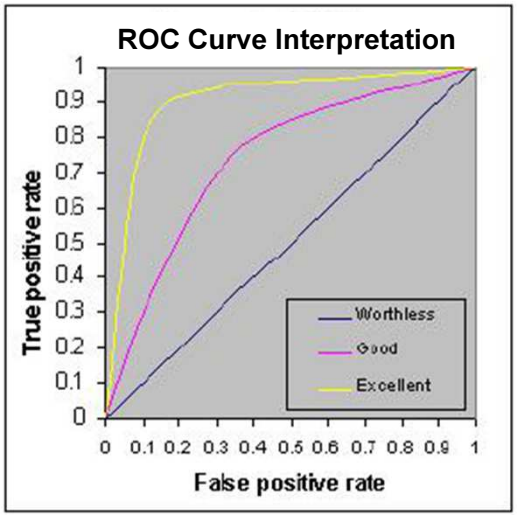
Study	Procalcitonin markers				C-reactive protein markers			
	No. of results		Sensitivity, % (95% CI)	Specificity, % (95% CI)	No. of results		Sensitivity, % (95% CI)	Specificity, % (95% CI)
	TP/FN	FP/TN			TP/ FN	FP/TN		
Aouifi et al.	46/2	8/41	96 (85–99)	84 (70–92)	50/33	4/10	60 (49–71)	71 (42–90)
Enguix et al.	19/3	1/23	86 (64–96)	96 (77–100)	19/4	1/22	83 (61–94)	96 (76–100)
Hatherill et al.	103/3	9/40	97 (91–99)	82 (68–91)	73/0	37/43	100 (95–100)	54 (42–65)
Muller	52/3	6/40	95 (84–99)	87 (73–95)	41/9	17/34	82 (68–91)	67 (52–79)
Penel et al.	43/14	0/5	75 (62–85)	100 (48–100)	43/24	0/1	64 (52–75)	100 (3–100)
Rothenburger et al.	12/2	3/42	86 (56–97)	93 (81–98)	14/30	1/14	32 (19–48)	93 (66–100)
Selberg et al.	19/5	3/6	79 (57–92)	67 (31–91)	19/9	3/2	68 (48–83)	40 (7–83)
Suprin et al.	49/6	26/14	89 (77–95)	35 (21–52)	55/5	19/14	92 (81–97)	42 (26–61)
Ugarte et al.	75/31	36/48	71 (61–79)	57 (46–68)	80/26	3/53	75 (66–83)	63 (52–73)
Viallon et al.	19/2	2/38	90 (68–98)	95 (82–99)	13/3	8/37	81 (54–95)	82 (67–91)
Total[b]	…	…	88 (80–93)	81 (67–90)	…	…	75 (62–84)	67 (56–77)

NOTE. FN, false negative; FP, false positive; TN, true negative, TP, true positive.

Simon L, et.al. Serum Procalcitonin and CRP Levels as Markers of Bacterial Infection: A Systematic Review and Meta-analysis. Clin Infect Dis 2004:39-206-217

sROC curves comparing procalcitonin and C-reactive protein as markers for detection of bacterial infections vs noninfective causes of inflammation.





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Procalcitonin and CRP as markers for bacterial versus viral infections.

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	TP/FN	FP/TN			TP/FN	FP/TN		
Hatherill et al.	103/6	9/8	94 (88–98)	47 (24–71)	73/2	36/12	97 (90–100)	25 (14–40)
Lorrot et al.	126/16	36/258	89 (82–93)	88 (83–91)	122/30	40/244	80 (73–86)	86 (81–90)
Schwarz et al.	11/0	5/14	100 (72–100)	74 (49–90)	14/6	1/8	70 (46–87)	89 (51–99)
Total[b]	…	…	92 (86–95)	73 (42–91)	…	…	86 (65–95)	70 (19–96)

NOTE. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Simon L, et.al. Serum Procalcitonin and CRP Levels as Markers of Bacterial Infection: A Systematic Review and Meta-analysis. Clin Infect Dis 2004:39-206-217

Procalcitonin and C-reactive protein levels as markers for bacterial versus viral infections

	PCT	CRP
Q value (95% CI)	89% (82%–96%)	83% (81%–85%)
Positive Likelihood ratio (95% CI)	6.05 (4.67-7.82)	3.75 (3.06-4.59)
Negative Likelihood ratio (95% CI)	0.10 (0.06–0.15)	0.20 (0.15–0.27)

The diagnostic accuracy of PCT is higher than CRP among hospitalized patients with suspected bacterial infections.

Simon L, et.al. Serum Procalcitonin and CRP Levels as Markers of Bacterial Infection: A Systematic Review and Meta-analysis. Clin Infect Dis 2004:39-206-217

Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis

Christina Wacker, Anna Prkno, Frank M Brunkhorst*, Peter Schlattmann*

Lancet Infect Dis 2013; 13: 426–35

Published Online February 1, 2013 http://dx.doi.org/10.1016/S1473-3099(12)70323-7

See Comment page 382

*Contributed equally

Department of Medical Statistics, Computer Sciences and Documentation (C Wacker Cand Med, A Prkno Cand Med, Prof P Schlattmann PhD), and Department of Anaesthesiology and Intensive Care Medicine (Prof F M Brunkhorst MD), Centre for Sepsis Control and Care, Jena University Hospital, Jena, Germany

Correspondence to: Prof Peter Schlattmann, Department of Medical Statistics, Computer Sciences and Documentation, Centre for

Summary

Background Procalcitonin is a promising marker for identification of bacterial infections. We assessed the accuracy and clinical value of procalcitonin for diagnosis of sepsis in critically ill patients.

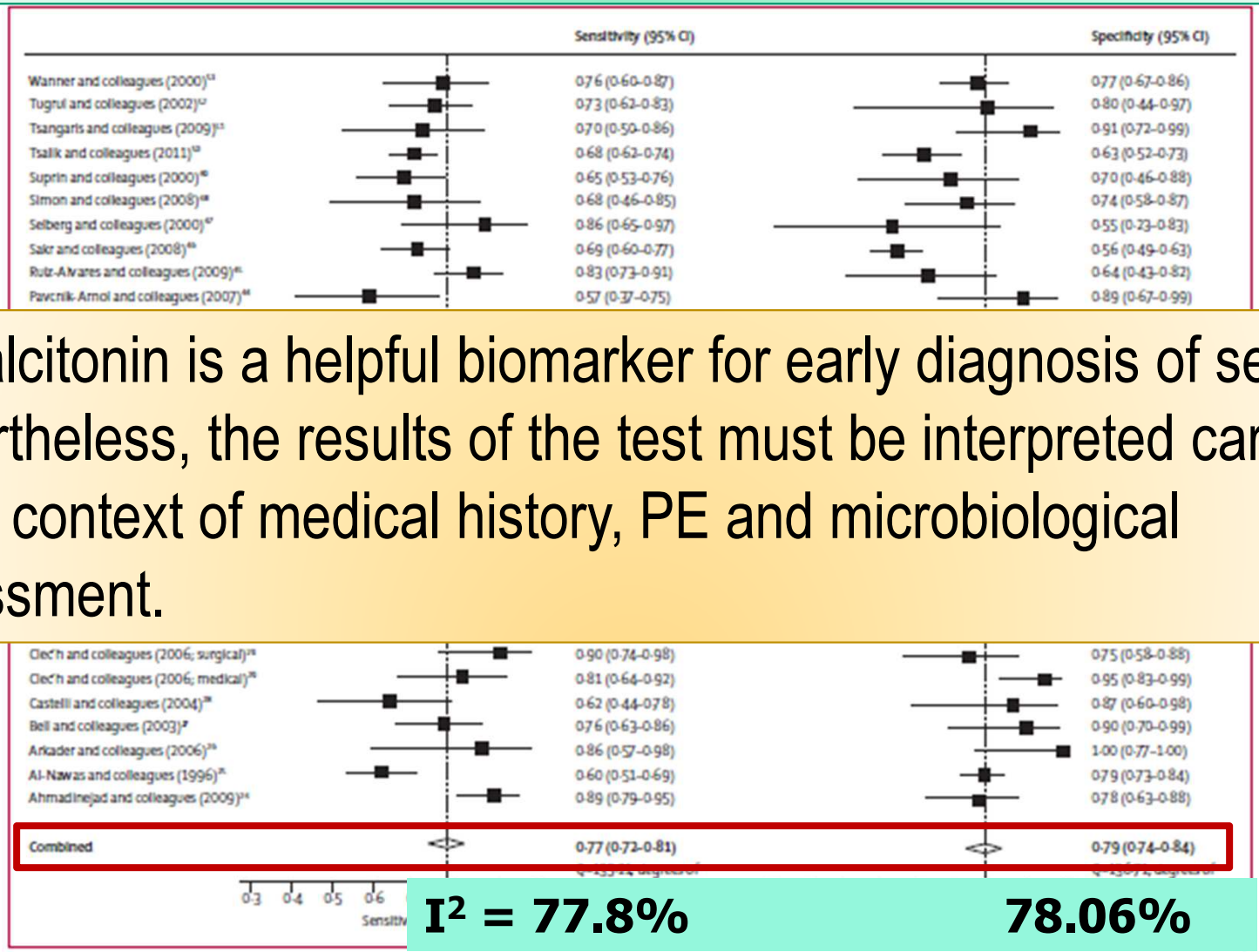
Methods We searched Medline, Embase, ISI Web of Knowledge, the Cochrane Library, Scopus, BioMed Central, and Science Direct, from inception to Feb 21, 2012, and reference lists of identified primary studies. We included articles written in English, German, or French that investigated procalcitonin for differentiation of septic patients—those with sepsis, severe sepsis, or septic shock—from those with a systemic inflammatory response syndrome of non-infectious origin. Studies of healthy people, patients without probable infection, and children younger than 28 days were excluded. Two independent investigators extracted patient and study characteristics; discrepancies were resolved by consensus. We calculated individual and pooled sensitivities and specificities. We used I^2 to test heterogeneity and investigated the source of heterogeneity by metaregression.

Findings Our search returned 3487 reports, of which 30 fulfilled the inclusion criteria, accounting for 3244 patients. Bivariate analysis yielded a mean sensitivity of 0·77 (95% CI 0·72–0·81) and specificity of 0·79 (95% CI 0·74–0·84). The area under the receiver operating characteristic curve was 0·85 (95% CI 0·81–0·88). The studies had substantial heterogeneity (I^2=96%, 95% CI 94–99). None of the subgroups investigated—population, admission category, assay used, severity of disease, and description and masking of the reference standard—could account for the heterogeneity.

Interpretation Procalcitonin is a helpful biomarker for early diagnosis of sepsis in critically ill patients. Nevertheless, the results of the test must be interpreted carefully in the context of medical history, physical examination, and microbiological assessment.

Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: A Systematic Review and meta-analysis. *Lancet Infect Dis* 2013: 13:426-35

Sensitivity and Specificity of Procalcitonin Assay in the Diagnosis of Sepsis



Procalcitonin is a helpful biomarker for early diagnosis of sepsis. Nevertheless, the results of the test must be interpreted carefully in the context of medical history, PE and microbiological assessment.

I^2 = 77.8% **78.06%**

Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: A Systematic Review and meta-analysis. *Lancet Infect Dis* 2013: 13:426-35

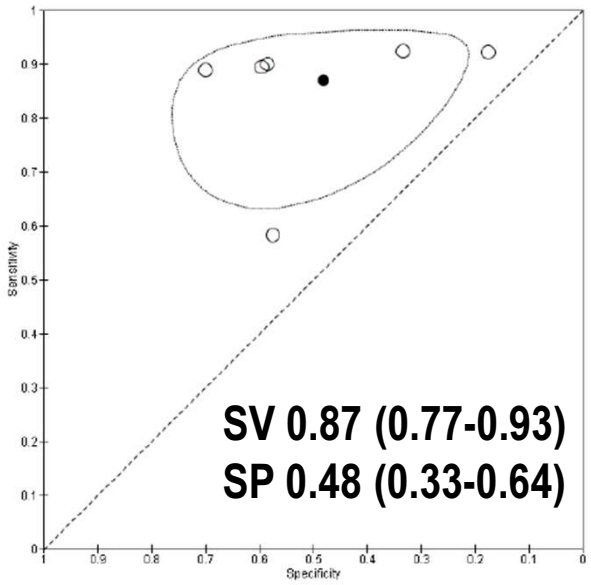
Acute Phase Reactants in Specific Infections

Clinical Infection	Acute Phase Reactant	Significance
Cellulitis	ESR>50 CRP>70	Higher predictive value of duration of hospital stay
Skin and Soft Tissue Infection	CRP>150	Higher likelihood of Necrotizing SSTI
Infective Endocarditis	CRP>122 PCT>0.5	Predictors of poor outcome PCT is a better marker for IE than CRP (SV 0.81; SP 0.85)
UTI	PCT>0.5	High likelihood of pyelonephritis and renal scar in children with UTI

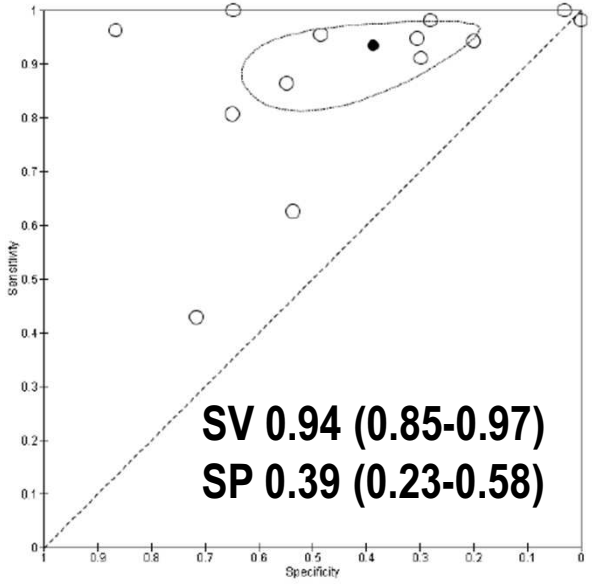
Markanday A. Acute Phase Reactants in Infections: Evidence -based review and a Guide For Clinicians. *Open Forum Infect Dis*. 2015

ESR, CRP and Procalcitonin in the diagnosis of Acute Pyelonephritis in Children

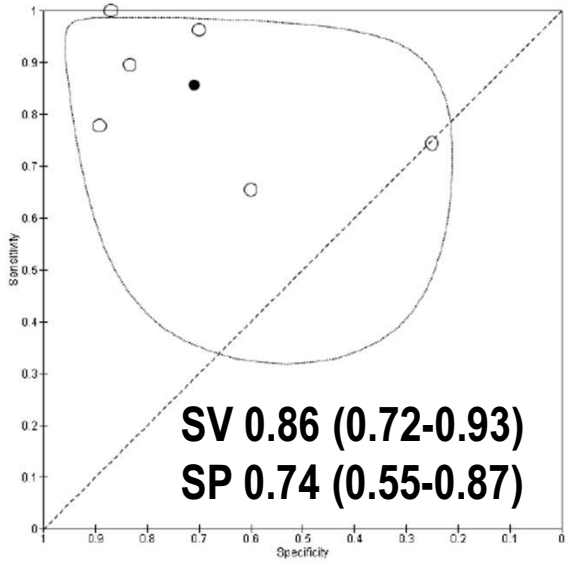
Summary ROC Plot of ESR, CRP and Procalcitonin



ESR > 30mm/hr



CRP> 20mg/ml



PCT > 0.5ng/ml

ESR, CRP, PCT do not appear to be sufficiently accurate in differentiating children with cystitis from those with pyelonephritis.

Shaikh et.al. Procalcitonin, CRP and ESR for the diagnosis of Acute Pyelonephritis in Children (Systematic Review) 2015 The Cochrane Collaboration. Published by John Wiley and Sons, Ltd.

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- **Overview of Acute Phase Reactants**
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  - Guide to Antibiotic Use: *ARI, Sepsis*
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CRP Guidance in Respiratory Infections

CRP value	Interpretation	Guide to antibiotic Therapy
< 20	Pneumonia extremely unlikely	Discourage antibiotic
20-50	Pneumonia very unlikely	Consider delayed prescribing
51-100	Possible pneumonia	Consider delayed prescribing
> 100	Severe infection Pneumonia very likely	Prescribe antibiotics immediately

Aabenhus et al. Biomarker as point-of-care tests to guide prescription of antibiotics in patients with ARI in primary care (Systematic Review). 2014 The Cochrane Collaboration.

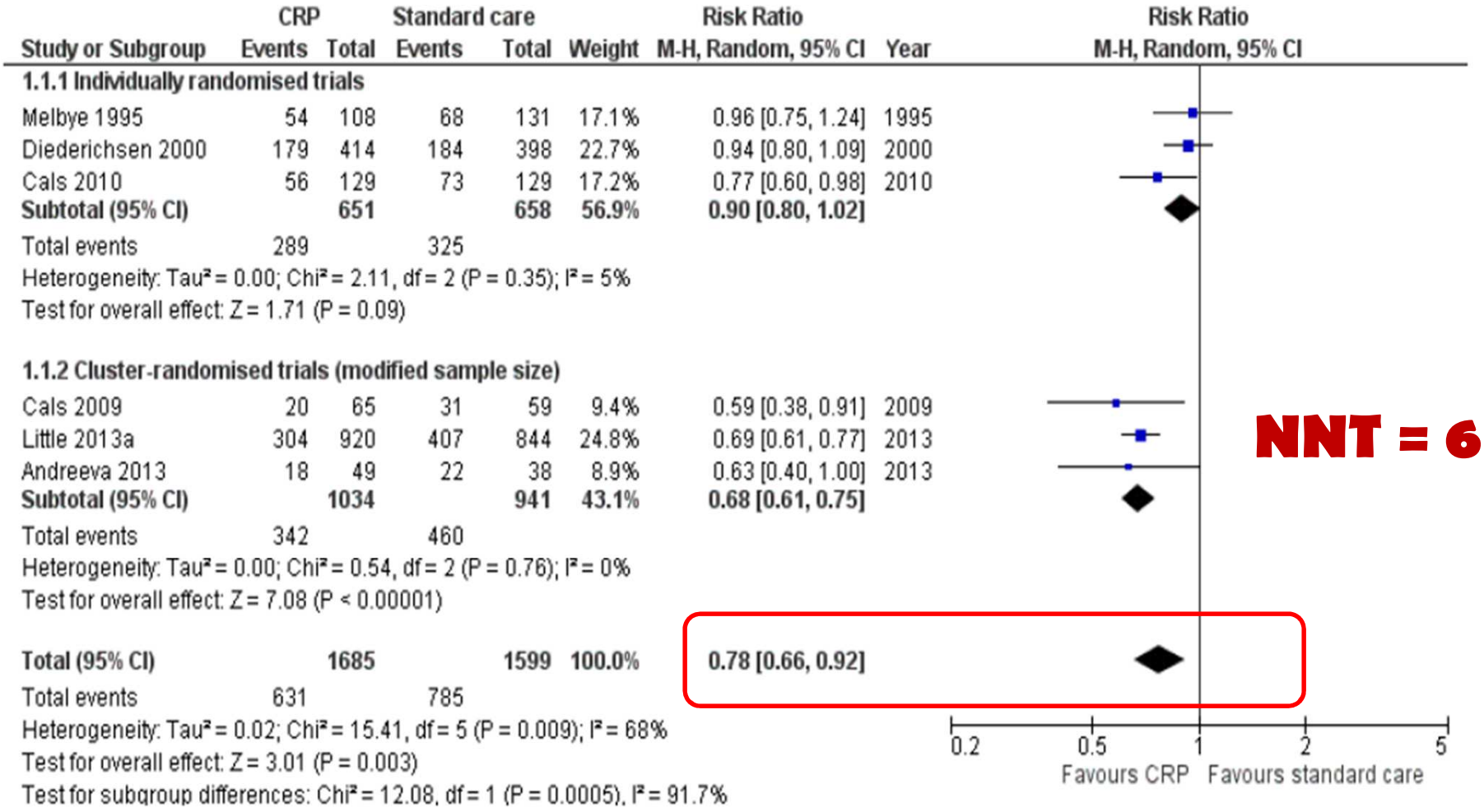
POINT-OF-CARE CRP COMPARED TO STANDARD CARE FOR GUIDING ANTIBIOTIC THERAPY IN ARI

Population: Patients with ARI
Settings: Primary Care
Intervention: CRP test
Comparison: Standard care

OUTCOMES	Comparative Risk		Effect R.R.(95% CI)	No. of participants (studies)	Quality of Evidence (GRADE)
	Standard	CRP			
No. of antibiotic prescriptions	IRCT 519/1000	467/1000	0.90 (0.8-1.02)	1309 (3)	Moderate
	CRCT 525/1000	357/1000	0.68 (0.61-0.75)	1975 (3)	
Clinical Recovery (7days)	414/1000	426/1000	1.03 (0.93-1.14)	1264 (3)	Moderate

Aabenhus et al. Biomarker as point-of-care tests to guide prescription of antibiotics in patients with ARI in primary care (Systematic Review). 2014 The Cochrane Collaboration.

Forest Plot of Comparison of Antibiotics Prescribed for ARI at Consultation: CRP vs Standard of Care



NNT = 6

Aabenhus et al. Biomarker as point-of-care tests to guide prescription of antibiotics in patients with ARI in primary care (Systematic Review). 2014 The Cochrane Collaboration.

Procalcitonin Guidance in Respiratory Infections

PCT value	Guide to antibiotic Therapy
< 0.10	Strongly discourage antibiotic
< 0.25	Discourage antibiotic
> 0.25	Encourage antibiotic
> 0.50	Strongly encourage antibiotic

Markanday A. Acute Phase Reactants in Infections: Evidence -based Review and a Guide For Clinicians. *Open Forum Infect Dis*. 2015

PROCALCITONIN ALGORITHM COMPARED TO STANDARD CARE FOR GUIDING ANTIBIOTIC THERAPY IN ARI

Population: Patients with ARI **Intervention Procalcitonin algorithm**
Settings: Primary Care, ER, ICU **Comparison: Standard care**

OUTCOMES	Comparative Risk		Relative Effect O.R.(95% CI)	No. of participants (studies)	Quality of Evidence (GRADE)
	Standard Care	Procalcitonin algorithm			
Mortality	60/1000	58/1000	0.91 (0.7-1.19)	4211 (14)	Moderate
Treatment Failure	219/1000	189/1000	0.83 (0.71-0.97)	4211 (14)	Moderate
Antibiotic exposure (mean)	8 days	3.47 days		4211 (14)	Moderate

Schuetz et al. Procalcitonin to initiate or discontinue antibiotics in ARI (Review)

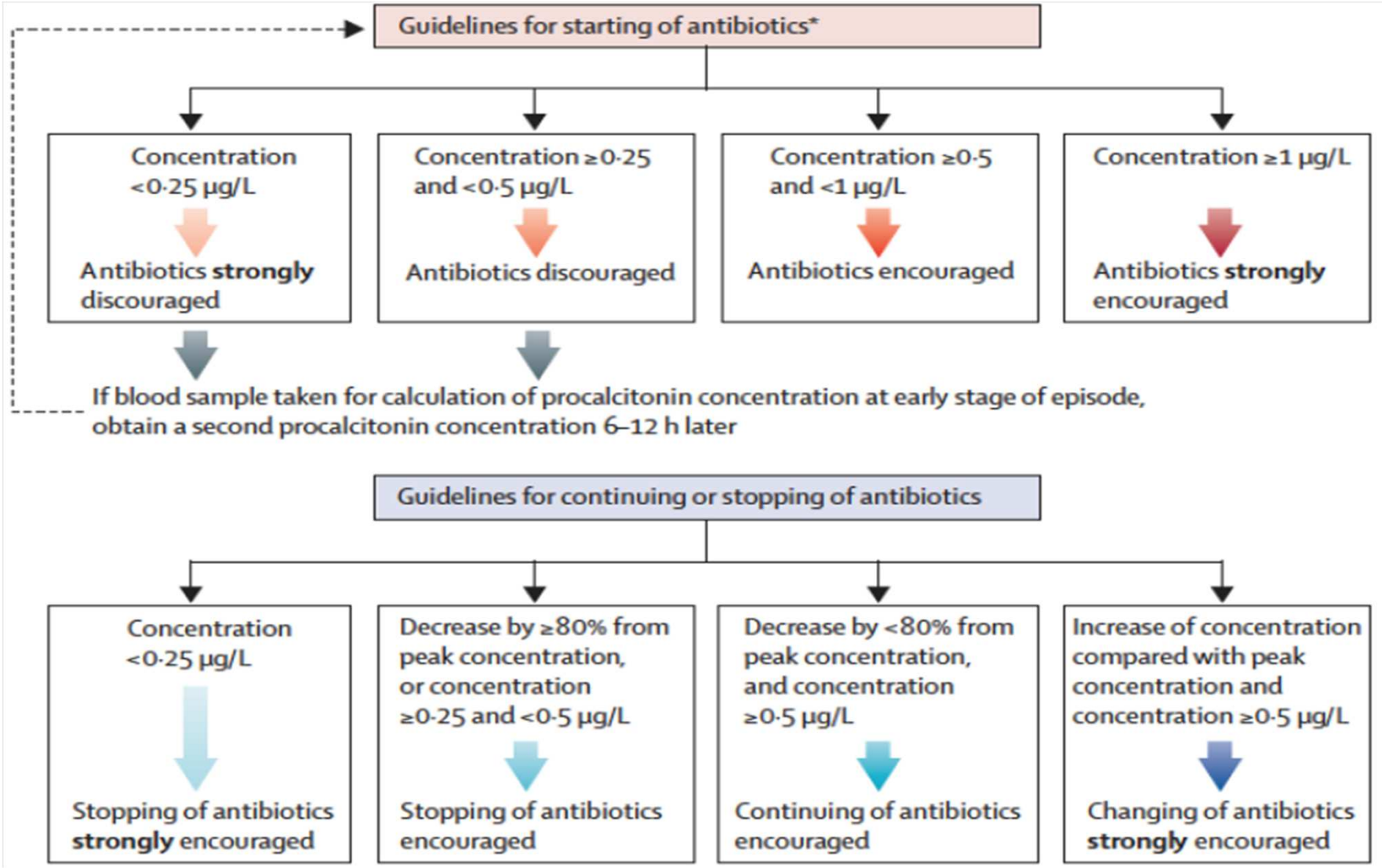
PROCALCITONIN GUIDANCE FOR SUSPECTED SEPSIS

In all unstable patients, initiate antibiotics immediately.

PCT Value (ng/mL)	Interpretation	Recommendation
0.1 – 0.5	Low likelihood for sepsis	Antibiotic discouraged
>0.5	Increased likelihood for sepsis	Antibiotic encouraged
>2.0	High risk of sepsis/ septic shock	Antibiotic strongly encouraged

Boudma et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): A Multicentre Randomised Controlled Trial. *Lancet*. 2010 Feb 6;375(9713):463-74.

PCT GUIDANCE FOR SUSPECTED SEPSIS: THE PRORATA TRIAL



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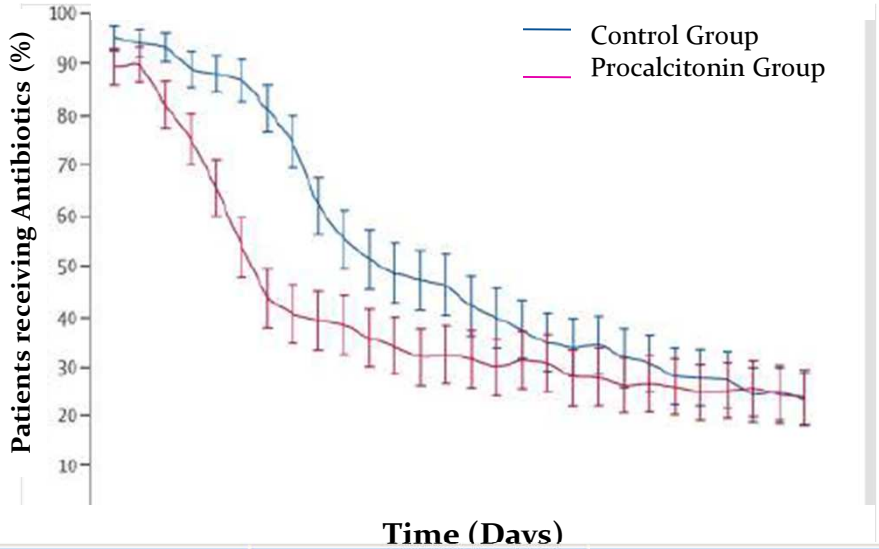
PCT GUIDANCE FOR SUSPECTED SEPSIS: THE PRORATA TRIAL



Evidence suggests that PCT guidance in ICUs decreases overall antibiotic use and has no significant effect on mortality and morbidity (based on length of hospital stay).

Boudma et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): A Multicentre Randomised Controlled Trial. *Lancet*. 2010 Feb 6;375(9713):463-74.

PCT-GUIDED DECISION-MAKING IN NEONATAL SEPSIS

Proportion of newborns treated with antibiotics:
Standard group (82%) ; PCT group (55%)
Absolute risk reduction 27%; OR 0.27 (95% CI 0.12–0.62)

Clinical outcome was similar and favorable in both groups.

Conclusion*:* PCT guidance shortens the duration of antibiotic therapy in infants with suspected early-onset sepsis.

Stocker M. Fontana M. el Helou S. Wegscheider K. Berger T.M. Use of Procalcitonin-Guided Decision-Making to Shorten Antibiotic Therapy in Suspected Neonatal Early-Onset Sepsis: Prospective Randomized Intervention Trial. *Neonatology* 2010;97:165–174

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- **Implications for Research**

Guideline Statements.... ARI

- Acute-phase reactants (ESR,CRP, PCT) cannot be used as the sole determinant to distinguish between viral and bacterial causes of CAP. **(Strong recommendation; High-quality evidence)**

- Acute-phase reactants need not be routinely measured in fully immunized children with CAP who are managed as outpatients. **(Strong recommendation; Low-quality evidence)**

- In patients with serious disease, APRs may be used in conjunction with clinical findings to assess response to therapy. **(Weak recommendation; Low-quality evidence)**

The Management of Community-Acquired Pneumonia in Infants and Children >3 months of age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011 Oct;53(7):e25-76.

Guideline Statements....SEPSIS

Avoiding routine use of antibiotics in the baby

Do not routinely give antibiotics to babies without risk factors for infection or clinical indicators or laboratory evidence of possible infection.

Investigations before starting antibiotics in the baby

When starting antibiotics in babies with risk factors for infection or clinical indicators of possible infection, perform a blood culture before administering the first dose.

Measure CRP at presentation when starting antibiotics in babies with risk factors for infection or clinical indicators of possible infection.

Neonatal infection: Antibiotics for Prevention and Treatment.
NICE Clinical guideline: 22 August 2012

Guideline Statements....SEPSIS

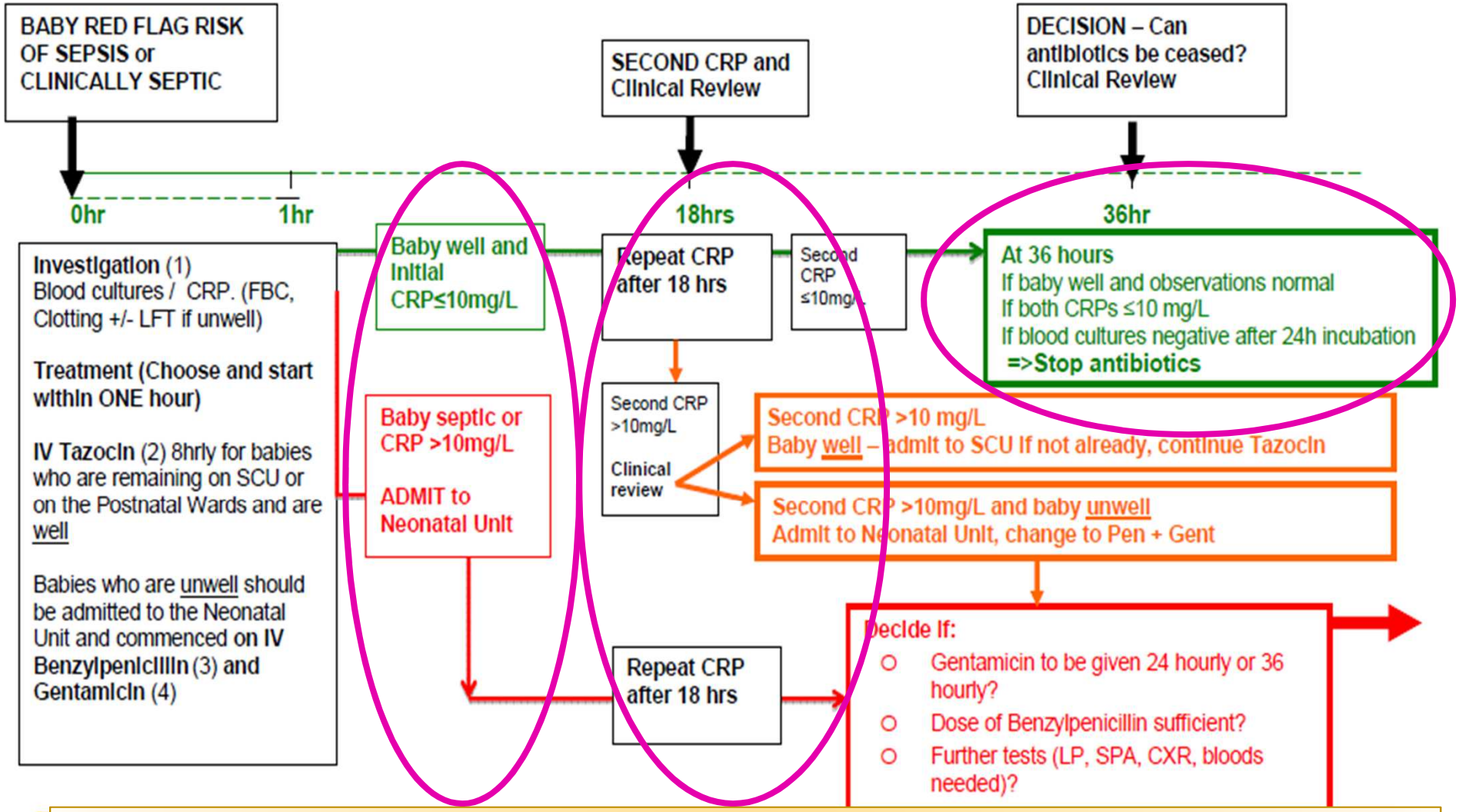
Duration of antibiotic treatment:

- In babies already given antibiotics, do CRP 18–24 hours after presentation.

- In babies given antibiotics, consider stopping the antibiotics at 36 hours if:
  - the blood culture is negative, and
  - the initial clinical suspicion of infection was not strong, and
  - the clinical condition is reassuring with no indicators of possible infection
  - the levels and trends of CRP are reassuring.

Neonatal infection: Antibiotics for Prevention and Treatment.
NICE Clinical guideline: 22 August 2012

Stages of Management of Baby at Risk of Early Onset Sepsis: Timeline



CRP is accepted as a useful test for ruling out an infection, monitoring treatment response and guiding duration of antibiotic therapy.

Guideline Statements....SEPSIS

A diagnosis of sepsis should be based on infection, documented or suspected, plus some of the following criteria:

1. General variables: T> 38.3°C or below 36°C; HR>90 /minute; rapid breathing; altered mental status; significant edema; and ↑blood sugar in the absence of diabetes.
2. Inflammatory variables: ↓↑WBC or >10% stabs; **↑CRP; ↑PCT.**
3. Haemodynamic and tissue perfusion variables: ↓BP; and ↑lactate
4. Organ dysfunction variables: ↓PaO2; ↓urine output; ↑creatinine; coagulation abnormalities; absent bowel sounds; ↓platelets; and ↑plasma bilirubin.

Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012
Procalcitonin testing for diagnosing and monitoring sepsis. NICE diagnostics guidance. October 2015

Implications for Research

1. Role of APRs in diagnosing IDs in immunosuppressed patients.
2. Comparison of APR guidance with other antibiotic-saving strategies.
3. Cost-effectiveness of antibiotic guidance strategies.
4. Multicenter trials involving heterogeneous patient groups to assess the effect of APR guidance on patient morbidity, mortality, antimicrobial stewardship and drug resistance.

POINTS TO REMEMBER

As a guide to ID diagnosis…

- ESR has limited value in ID diagnosis but helpful in monitoring treatment response.
- CRP is a useful adjunct in differentiating pneumonia from other ALRTI.
- In neonatal sepsis, CRP is more accurate if done serially.
- PCT is a more accurate marker for bacterial infections than CRP.
- PCT is a helpful marker for sepsis. However, it must be interpreted within the context of a careful history, PE and other labs.
- CPGs on ARI and Sepsis acknowledge the importance of APRs in disease diagnosis and management.

POINTS TO REMEMBER

As guide to antibiotic use…

- In ARI:
  - CRP guidance reduces antibiotic … ect recovery and duration of ill…
  - PCT guidance red… with no increase in mortality or …
- In s… is useful in the management of neonatal sepsis.
  - PCT guidance decreases antibiotic use with no ill effect on patient outcome.

Decisions on antibiotic use should not be based solely on APRs.

Diagnosis is not the end, but the beginning of practice.

~Martin H. Fischer (1879-1962)

Thank You