Why Procalcitonin

Dr Brajagopal Roy

Introduction

- Infection accounts for - estimated 11% of neonatal deaths and 20% of deaths in infants and children.
- Our Aim - To identify children with serious bacterial infection (SBI) and invasive bacterial infection (IBI)
- To avoid overtreatment and maintain standards of antimicrobial stewardship
- More accurate diagnostic tests
- One such test could well be procalcitonin (PCT).

Physiological background

- PCT - a prohormone of calcitonin - released by the parafollicular (C cells) of the thyroid
- It reduces serum calcium levels
- If serum ionised calcium is high - PCT is cleaved to calcitonin
- It is also released in response to certain infectious and inflammatory stimuli
- PCT is encoded by the *CALC1* gene, which under physiological conditions is solely expressed by neuroendocrine tissues
- In non-physiological states (such as bacterial infection), *CALC1* is also expressed by non-neuroendocrine tissues - which leads to serum PCT levels that are hundreds or even thousands of times higher than normal
- *in vivo* studies suggest that it may have a role as a driver of the inflammatory response to bacterial infection and is associated with worsened symptoms and increased mortality.

Technicality

- **How to sample?**
- PCT is measured from a plasma sample collected in a lithium heparin sample bottle. It can be stored for up to 4 hours at room temperature. The minimum volume of blood required is between 20 and 200 µL. Semiquantitative and quantitative assays using smaller volumes of whole blood from finger prick samples are also available.
- **When to sample?**
- PCT levels start to rise 2 hours after the start of a septic insult and peak by 12 hours. It has a half-life of approximately 24 hours and levels decline to normal values between 48 and 72 hours.
- **How is the sample processed?**
- There are several commercially available PCT assays, all of which use immunoassay technology. This involves detection of antibody complexes that bind PCT proteins in serum.
- Qualitative, semiqualitative and quantitative assays are available. Sample processing times range from 18 to 29 min. The maximum level of PCT also varies between assays (100–5000 ng/mL). Cut-off values for PCT in suspected sepsis are widely debated - they typically range from 0.3 to 1 ng/mL (µg/L).

Febrile child

In a febrile child, does a low PCT rule out IBI?

Febrile infants under 3 months

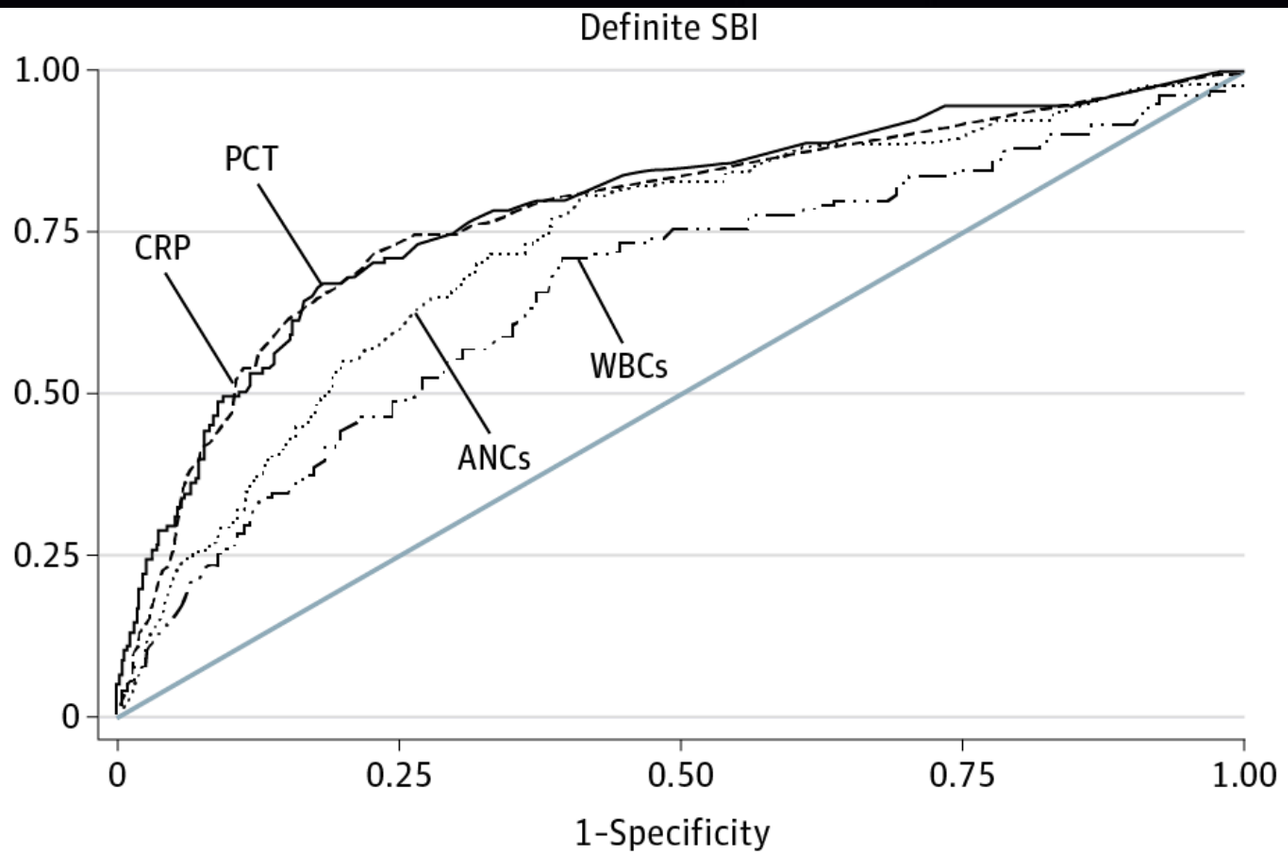
- **Olaciregui *et al*** - The sample comprised 347 patients (23.63% with SBI). Mean PCT, CRP, leucocyte and neutrophil count were significantly higher in the group with SBI

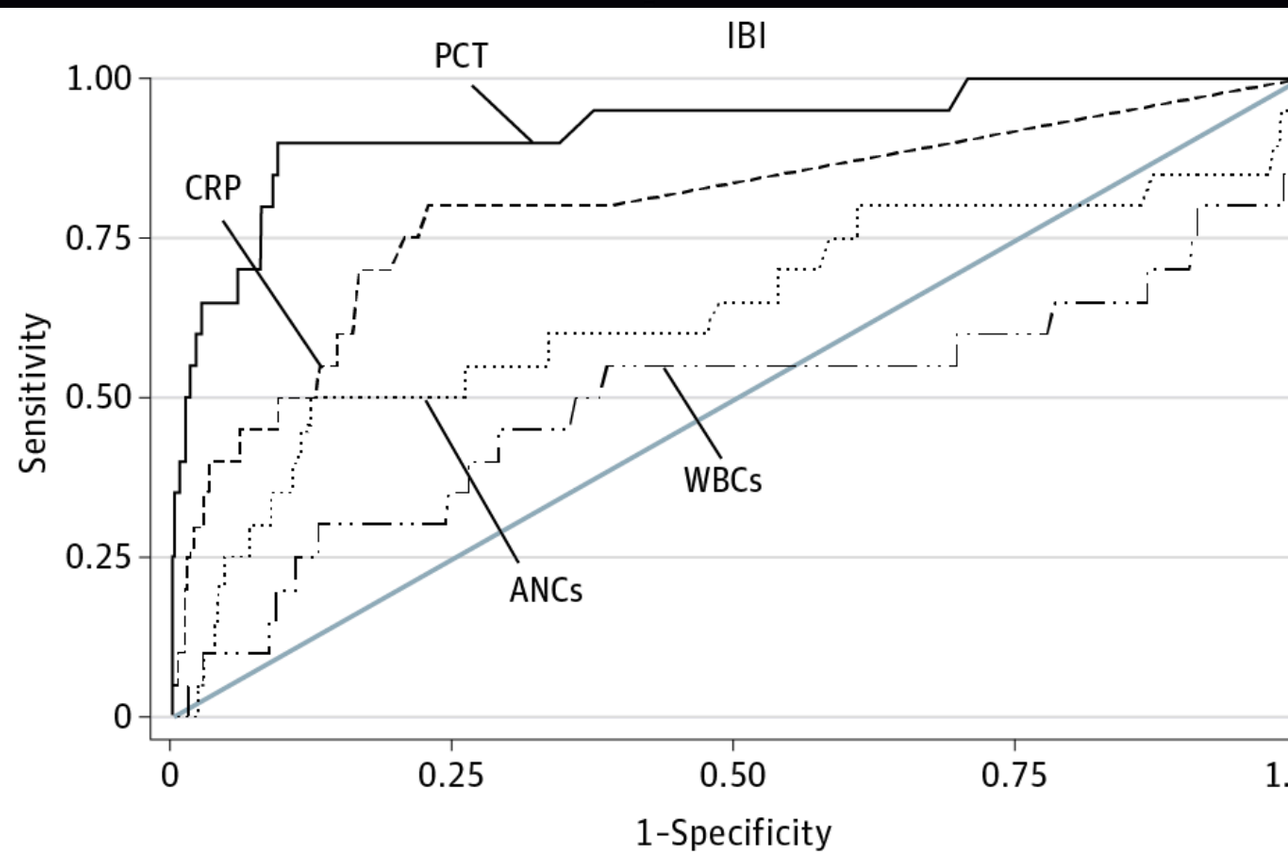
- In the 15 infants with more invasive bacterial infections (sepsis, bacteraemia, bacterial meningitis), the diagnostic value of PCT (AUC 0.84, 95% CI 0.79 to 0.88) was higher than CRP (AUC 0.68, 95% CI 0.63 to 0.73).

- In infants who had been febrile for under 12 h, the differences between PCT, CRP and leucocyte count were statistically significant in both SBI and non-SBI groups, with increasing predictive value of PCT and decreasing value of CRP.

- **Gomez *et al*** - report that in infants less than 3 months of age with fever and a negative urine dip test, a PCT of <0.5 ng/mL has a negative likelihood ratio (NLR) of 0.25 for IBI.

- **Milcent *et al-*** recruited over 2000 febrile infants less than 3 months of age presenting to the emergency department. They report an NLR of 0.1 for bacteraemia and bacterial meningitis in infants with a PCT of <0.3 ng/mL, demonstrating that a negative PCT markedly reduced the post-test probability of an IBI in a well-looking febrile infant.





	Definite SBI (n = 139)		IBI (n = 21)	
Biomarker	AUC (95% CI)	*P* Value*	AUC (95% CI)	*P* Value*
PCT, ng/mL	0.81 (0.75-0.86)		0.91 (0.83-0.99)	
CRP, mg/L	0.80 (0.75-0.85)	.70	0.77 (0.65-0.89)	.002
ANCs, /μL	0.73 (0.66-0.79)	.08	0.61 (0.45-0.77)	.004
WBCs, /μL	0.66 (0.58-0.73)	<.001	0.48 (0.31-0.66)	<.001

*Compared with PCT.

Febrile infants

- Most compelling evidence suggest PCT is far better than current markers - CRP and white cell count
- But most authors comment that an NLR of 0.1 remains too high to use PCT independently
- On the basis of the available evidence, a serum PCT level < 0.3 ng/mL significantly reduces the likelihood that a febrile child has an IBI.
- However, the studies unanimously conclude that PCT should not be used as the sole criterion to exclude potential IBIs.
- Rather, it should be interpreted in the context of both clinical evidence and other laboratory tests.

Febrile neutropenia

In a subset of paediatric oncology patients with febrile neutropenia, meta-analysis of CRP, PCT and interleukin-8 reported

that study protocols were too heterogeneous to make any reliable conclusions about the effectiveness of these biomarkers either in the diagnosis of bacterial infection or in monitoring response to antibiotics

There is insufficient evidence at present to guide the use of PCT in children with febrile neutropenia.

Pneumonia

- Clinical assessment, conventional blood tests and radiographs cannot reliably differentiate between viral and bacterial causes of lower respiratory tract infection (LRTI) and pneumonia.

- ProPAED was a randomised trial designed to assess the use of PCT in the antibiotic management of LRTI and pneumonia, involving 337 children with a mean age of 3.8 years.

- It asked three key questions; first, can PCT reduce antibiotic prescribing rates? Second, can PCT monitoring reduce the duration of antibiotic therapy and, third, can PCT reliably predict response to antibiotic therapy?

1. Baer G , Baumann P , Buettcher M , *et al* . Procalcitonin guidance to reduce antibiotic treatment of lower respiratory tract infection in children and adolescents (ProPAED): a randomized controlled trial. *PLoS One* 2013;**8**:e68419.doi:10.1371/journal.pone.0068419

Outcome	Measure	PCT group (N = 168)		Control group (N = 169)		Rate difference, % (95% CI)	Odds ratio (95% CI)	Mean difference (95% CI)
Primary endpoint			*		*			
Antibiotic prescription within 14 days of randomization	N (%)	104 (62)		93 (56)	(N = 165)	6 (−5, 16)	1.26 (0.81, 1.95)	
Secondary endpoints								
Duration of antibiotic treatment, days	Mean (median [IQR])	4.5 (4 [0–8])	(N = 167)	6.3 (6 [0–11])	(N = 164)			−1.8 (−3.1, −0.5)
Antibiotic side effects*	N (%)	56 (39)	(N = 144)	57 (38)	(N = 149)	1 (−10, 12)	1.03 (0.64, 1.65)	
Duration of antibiotic side effects, days	Mean (median [IQR])	1.4 (0 [0–2])	(N = 144)	1.3 (0 [0–1])	(N = 149)			0.1 (–0.4, 0.7)
Hospitalization	N (%)	104 (62)		100 (60)	(N = 167)	2 (−8, 12)	1.09 (0.70, 1.69)	
Duration of hospitalization, days	Mean (median [IQR])	2.6 (2 [0–4])	(N = 167)	2.7 (2 [0–5])	(N = 164)			−0.1 (−0.8, 0.5)
Safety†	N (%)	38 (23)		33 (20)	(N = 164)	2 (−6, 11)	1.16 (0.69, 1.97)	

*On days of antibiotic therapy patients showing an exanthema or vomiting or diarrhea as stated in the patient's diary from day 1 up to day 14.
†Occurrence of any of the following entities: **complications** from pneumonia or other LRTI (e.g., parapneumonic effusions in need of puncture, empyema, lung abscess, necrotizing pneumonitis, acute respiratory distress syndrome) or occurrence of **SAEs** (hospital readmission, admission to intensive care unit, unexpected life threatening condition, condition of compromising sequelae or death occurring in the 14 days following the inclusion of the patient) or **disease specific failure**, including hospital readmission, recurrent infection in need of antibiotics or development of any co-morbid condition in need of antibiotics irrespective of the primary LRTI diagnosis, worsening of ≥20% of daily restrictions from LRTI according to parent interview and diary, new onset of respiratory distress or worsening of pre-existing respiratory distress (i.e., tachypnea, and or dyspnea in spite of β_2-mimetic treatment) or increasing or new onset of O_2 requirement or development of global respiratory insufficiency – increasing pCO_2. * number of individuals with available data for a given endpoint.
doi:10.1371/journal.pone.0068419.t002

PCT guidance reduced antibiotic exposure by reducing the duration of antibiotic treatment, while not affecting the antibiotic prescribing rate. The latter may be explained by the low baseline prescribing rate in Switzerland for pediatric LRTI and the choice of an inappropriately low PCT cut-off level for this population.

1. Baer G , Baumann P , Buettcher M , *et al* . Procalcitonin guidance to reduce antibiotic treatment of lower respiratory tract infection in children and adolescents (ProPAED): a randomized controlled trial. *PLoS One* 2013;**8**:e68419.doi:10.1371/journal.pone.0068419

Outcome	Measure	PCT group (N = 168)		Control group (N = 169)	
Primary endpoint			*		*
Antibiotic prescription within 14 days of randomization	N (%)	104 (62)		93 (56)	(N = 165)
Secondary endpoints					
Duration of antibiotic treatment, days	Mean (median [IQR])	4.5 (4 [0–8])	(N = 167)	6.3 (6 [0–11])	(N = 164)
Antibiotic side effects*	N (%)	56 (39)	(N = 144)	57 (38)	(N = 149)
Duration of antibiotic side effects, days	Mean (median [IQR])	1.4 (0 [0–2])	(N = 144)	1.3 (0 [0–1])	(N = 149)
Hospitalization	N (%)	104 (62)		100 (60)	(N = 167)
Duration of hospitalization, days	Mean (median [IQR])	2.6 (2 [0–4])	(N = 167)	2.7 (2 [0–5])	(N = 164)
Safety†	N (%)	38 (23)		33 (20)	(N = 164)

*On days of antibiotic therapy patients showing an exanthema or vomiting or diarrhea as stated in the patient's diary from day 1 up to day 14

†Occurrence of any of the following entities: **complications** from pneumonia or other LRTI (e.g., parapneumonic effusions in need of punctur syndrome) or occurrence of **SAEs** (hospital readmission, admission to intensive care unit, unexpected life threatening condition, condition of comp patient) or **disease specific failure**, including hospital readmission, recurrent infection in need of antibiotics or development of any co-morbid co of ≥20% of daily restrictions from LRTI according to parent interview and diary, new onset of respiratory distress or worsening of pre-existing respi increasing or new onset of O_2 requirement or development of global respiratory insufficiency – increasing pCO_2. * number of individuals with

doi:10.1371/journal.pone.0068419.t002

PCT guidance reduced antibiotic exposure by reducing the duration of antibiotic treatment, while not affecting the antibiotic prescribing rate. The latter may be explained by the low baseline prescribing rate in Switzerland for pediatric LRTI and the choice of an inappropriately low PCT cut-off level for this population.

Respir Med. 2011 Dec;105(12):1939-45. doi: 10.1016/j.rmed.2011.09.003. Epub 2011 Sep 29.
Procalcitonin measurements for guiding antibiotic treatment in pediatric pneumonia.
Esposito S1, Tagliabue C, Picciolli I, Semino M, Sabatini C, Consolo S, Bosis S, Pinzani R, Principi N.

Study in Italy involving 314 children hospitalised with uncomplicated CAP - age group 1-14 years

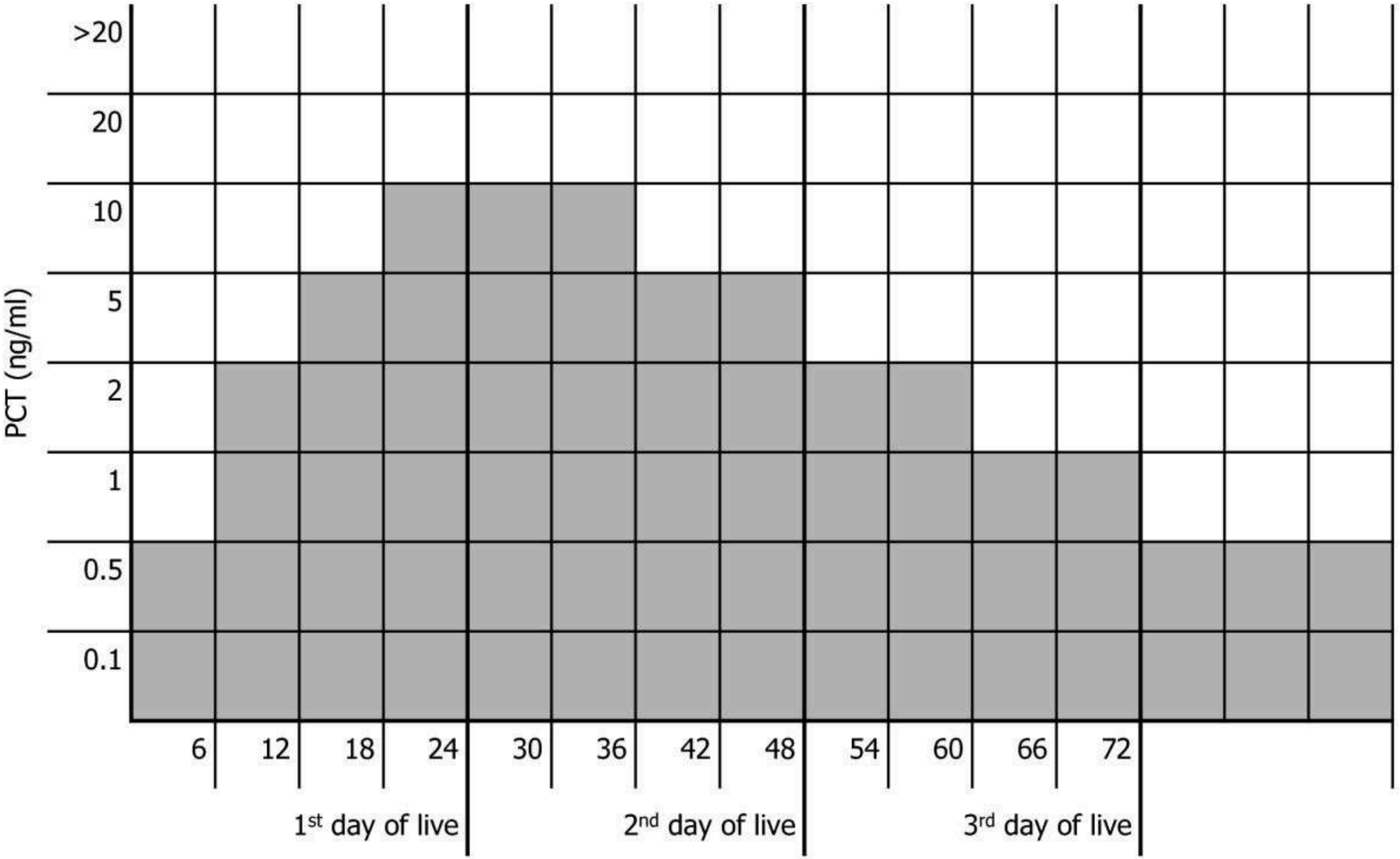
In comparison with the controls, the PCT group received significantly fewer antibiotic prescriptions (85.8% vs 100%; $p < 0.05$), were exposed to antibiotics for a shorter time (5.37 vs 10.96 days; $p < 0.05$), and experienced fewer antibiotic-related adverse events (3.9% vs 25.2%; $p < 0.05$), regardless of CAP severity.

Neonatal sepsis

- PCT levels need to be interpreted with caution as they vary according to gestational age at birth

- And also the time of sampling particularly over the first 48 hours (when there is a physiological increase in serum PCT levels). Peak physiological PCT levels may not be reached until 48 hours of life.

- Although attempts have been made to produce a nomogram for neonatal PCT measurements over the first 48 hours of life, the numbers have been too low to validate the test's performance


PCT (ng/ml)
>20
20
10
5
2
1
0.5
0.1
6
12
18
24
30
36
42
48
54
60
66
72
1st day of live
2nd day of live
3rd day of live

Altunhan H , Annagür A , Örs R , *et al* . Procalcitonin measurement at 24 hours of age may be helpful in the prompt diagnosis of early-onset neonatal sepsis. *Int J Infect Dis* 2011;**15**:e854–8.doi:10.1016/j.ijid.2011.09.007

	PCT at birth	PCT at 24 h of life	CRP at birth	CRP at 24 h of life
Cutoff	≥0.59 ng/ml	≥5.38 ng/ml	>5 mg/l	>12 mg/l
Sensitivity, % (95% CI)	48.7 (39.45–57.89)	83.3 (76.28–90.08)	44.5 (33.59–56.77)	76.4 (68.18–85.28)
Specificity, % (95% CI)	68.6 (58.62–75.91)	88.6 (79.41–92.27)	59.4 (51.35–71.58)	78.9 (67.23–87.76)
PPV	48.71	83.33	45.62	79.75
NPV	68.57	88.57	64.25	81.62

Early Neonatal sepsis

- Based on current evidence, PCT alone should not be used to exclude bacterial infection in the newborn.
- However there is a potential role for PCT to guide duration of antibiotic usage in early-onset suspected sepsis.

- In a trial of 121 term newborns with EONS, serial PCT monitoring resulted in a 27% absolute reduction in the number of newborns receiving antibiotics ≥72 hours and reduced the mean duration of antibiotic exposure by 22 hours with comparable clinical outcomes and number of adverse effects.

- All babies underwent risk stratification prior to treatment based on history and clinical assessment, perhaps unsurprisingly, the benefit of PCT was greatest in neonates stratified into the lower risk group

-

Lancet. 2017 Aug 26;390(10097):871-881. doi: 10.1016/S0140-6736(17)31444-7. Epub 2017 Jul 12.

Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPIns).

Stocker M1, van Herk W2, El Helou S3, Dutta S3, Fontana MS1, Schuerman FABA4, van den Tooren-de Groot RK5, Wieringa JW6, Janota J7, van der Meer-Kappelle LH8, Moonen R9, Sie SD10, de Vries E11, Donker AE12, Zimmerman U13, Schlapbach LJ14, de Mol AC15, Hoffman-Haringsma A16, Roy M17, Tomaske M18, Kornelisse RF19, van Gijsel J20, Visser EG21, Willemsen SP22, van Rossum AMC21; NeoPInS Study Group.

- Between May 21, 2009, and Feb 14, 2015, - 1710 neonates were enrolled and randomly assigned to either procalcitonin-guided therapy (n=866) or standard therapy (n=844).

- 1408 neonates underwent per-protocol analysis (745 in the procalcitonin group and 663 standard group).
- For the procalcitonin group, the duration of antibiotic therapy was reduced (intention to treat: 55·1 *vs* 65·0 h, p<0·0001; per protocol: 51·8 *vs* 64·0 h; p<0·0001).

- Interpretation
- Procalcitonin-guided decision making was superior to standard care in reducing antibiotic therapy in neonates with suspected early-onset sepsis.

Clinical applications of procalcitonin under evaluation in children

- Diagnosis of sepsis (due to bacterial infection) in neonates, infants and children.
- Identifying bacterial aetiology in lower respiratory tract infection or pneumonia.
- Diagnosis of sepsis (due to bacterial infection) in HDU and ITU environments.
- Identification of pyelonephritis in febrile children with UTI.
- Risk of vesicoureteric reflux (VUR) and reflux nephropathy in children with UTI.
- Differentiation of bacterial and viral meningitis.
- Guiding duration of antibiotic therapy in suspected sepsis, LRTI/pneumonia and meningitis.
- Monitoring neonates and children at risk of postoperative infections.

Conclusion

- Serum procalcitonin levels are higher in bacterial infections involving the bloodstream, lower respiratory tract, cerebrospinal fluid and urine than viral infections.
- Procalcitonin-guided therapy has been shown to reduce the duration of antibiotic therapy for children with lower respiratory tract infection, pneumonia and febrile illness.
- Although it can aid in decision-making, a low serum procalcitonin does not exclude the possibility of bacterial meningitis or bacteraemia.