

Procalcitonin as an early marker of infection in neonates and children

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A child or neonate presenting with fever is a common medical problem. To differentiate between those with a severe bacterial infection and those with a localised bacterial or a viral infection can be a challenge. This review provides an overview of neonatal and paediatric studies that assess the use of procalcitonin as an early marker of bacterial infection. Procalcitonin is an excellent marker for severe, invasive bacterial infection in children. However, the use of procalcitonin in the diagnosis of neonatal bacterial infection is complicated, but if correctly used procalcitonin results in a higher specificity than C-reactive protein. In addition, procalcitonin has been shown to correlate with severity of disease (urinary tract infections and sepsis), and can therefore be used as a prognostic marker. Procalcitonin is therefore a useful additional tool for the diagnosis of bacterial disease in neonates and children.

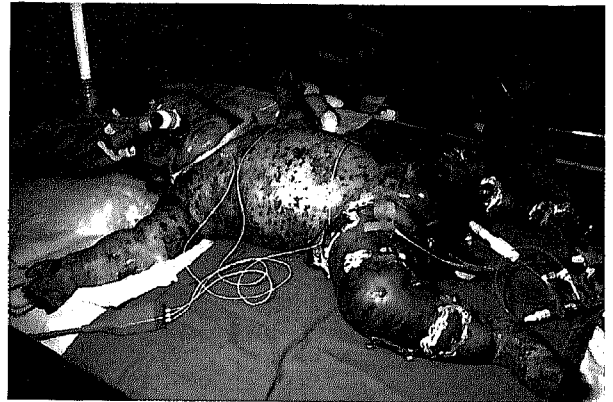


Figure 1. Infant with meningococcal purpura (courtesy of J A Hazelzet, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, Netherlands).

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The child or neonate who presents with fever is a common problem in paediatric practice. Even for very experienced paediatricians it is a challenge to tell the difference between neonates or children at risk for a severe bacterial infection and those with a localised bacterial or viral infection. Rapid diagnosis and treatment of systemic bacterial infections is essential in neonates, infants, and children, since a delay in the treatment of severe bacterial infections may lead to a poorer outcome (figure 1). However, it is important to limit the use of antibiotics to reduce the development of resistance of bacteria to antibiotics, to reduce complications and costs, and to prevent unnecessary admission to hospital for the administration of parental antibiotics in viral infections.

C-reactive protein (CRP) is an acute-phase protein released by the liver after the onset of inflammation or tissue damage. This protein is frequently used to differentiate between viral and bacterial infections. However, CRP is neither highly specific nor sensitive for bacterial infection since it can remain at low concentrations in bacterial infections and can increase significantly in viral infections.^{1,2} In addition, CRP concentrations do not increase until 12 h after the onset of fever. In 1993, Assicot and colleagues³ reported high concentrations of procalcitonin in sera of children during septic conditions. Procalcitonin also seemed to correlate with the severity of microbial invasion and decreased rapidly during antibiotic therapy.^{4,5} Since 1993, many studies have assessed the use of procalcitonin as a marker of bacterial infection in adults, children, and neonates.^{6–8}

Procalcitonin is a 116-aminoacid peptide and one of the precursors of calcitonin. The physiological function of calcitonin remains unknown. No disorders attributable to either an excess or a deficiency of calcitonin have been identified. Microbial infections induce a ubiquitous increase in *CALC1* gene expression and a subsequent release of calcitonin precursors from all tissues and cell types throughout the body.⁹ In bacterial infections, procalcitonin increases from concentrations in the picogram range (below the detection level of current procalcitonin assays) to plasma concentrations ranging from 1 to 1000 ng/mL. This increase often correlates with the severity of the disease and with mortality.^{3,10–12} Increases in procalcitonin occur more rapidly than increases in CRP. Procalcitonin can be detected in the plasma 2 h after the injection of endotoxins. Within 6–8 h, procalcitonin concentrations rise and a plateau is reached after approximately 12 h.¹³ CRP can be detected in the plasma after 12 h and reaches a plateau after 20–72 h. Procalcitonin and CRP decrease to their normal values after 2–3 days and 3–7 days, respectively.^{14–16} This rapid and specific induction of procalcitonin after an adequate stimulus, and the high and reliable production of procalcitonin in patients with severe bacterial infections

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or sepsis, suggests a pathophysiological function of procalcitonin in the acute immune response. Currently, it is not clear whether procalcitonin is a cytokine, a hormone, or an acute-phase protein since it has characteristics of all these mediators.

Procalcitonin can be measured with a quantitative immunoluminometric assay (LUMItest PCT, Brahms Diagnostica, Berlin, Germany) in 2 h, with a maximum interassay variation of approximately 0.3 ng/mL. A rapid semiquantitative chromatographic test (Brahms PCT-Q, Brahms Diagnostica), which can be used at the bedside by physicians or nurses, gives an indication of procalcitonin concentration (in bands of <0.5 ng/mL, 0.5–2 ng/mL, 2–10 ng/mL, and >10 ng/mL) in 30 min.

This review provides an overview of all neonatal and paediatric clinical studies published up to December 31, 2003, that assessed procalcitonin as a marker of bacterial infection, and seeks to answer the question of whether procalcitonin is more valuable as a marker for bacterial infection in neonatal infections, invasive infections, infections of the lower respiratory tract, urinary tract infections (UTIs), fever of unknown origin, and in paediatric oncology than the more frequently used CRP.

Neonatal infections

Infection in neonates is a major cause of morbidity and mortality. The infection itself is difficult to identify solely on the basis of physical findings because signs are non-specific and may be absent when the infant is infected just before delivery.¹⁷ The value of procalcitonin as a marker for bacterial infection in neonates is complicated by a physiological increase of procalcitonin during the first days of life. An increase in procalcitonin concentrations was reported in healthy newborn neonates, before term and at term, with a peak at 18–30 h of life, thereafter reverting to

normal at 42–48 h.^{18–21} The adult reference range applies from 3 days after birth (figure 2).^{19–21} Assumma and colleagues²² hypothesised that the postnatal increase in procalcitonin indicates transplacental passage of maternal procalcitonin. However, higher procalcitonin concentrations were seen in cord sera than in paired maternal samples at birth. Even larger differences were found at 24 h and 48 h of age. The investigators therefore concluded that the postnatal increase of procalcitonin cannot be explained by transplacental passage.

Results of studies on the use of procalcitonin as an early marker of neonatal sepsis are contradictory (table 1). A significant increase in serum procalcitonin concentration during sepsis was found in both term neonates and a heterogeneous group of preterm neonates. This increase did not seem to be dependent on gestational age.^{18–20,23,25,28,29,36} These studies seem to show that procalcitonin is an early and specific marker of severe sepsis, by contrast with CRP. They confirm the importance of this marker in excluding infection shortly after birth.

However, six studies have concluded that procalcitonin is not a better early marker for neonatal sepsis than CRP.^{20,27,30,33–35} The lack of specificity was explained in part by significantly higher procalcitonin in non-infected infants with respiratory distress syndrome or haemodynamic failure than in non-infected infants who had neither of these conditions.^{20,35} Bonac and colleagues³³ reported that neonates with either perinatal asphyxia, intracranial haemorrhage, pneumothorax, or after resuscitation had raised serum procalcitonin concentrations that did not differ from those of septic neonates up to 48 h after onset of clinical signs of distress or infection. Hypoxaemia, which is common to the different conditions of neonatal distress, could be responsible for increased procalcitonin concentrations.^{18,41} Prepartum and intrapartum administration of antibiotics may affect the concentration of procalcitonin in the umbilical cord,⁴² and postnatal administration of antibiotics will definitely influence postnatal procalcitonin concentrations. Prenatal, intranatal, and postnatal administration of antibiotics may therefore be a major confounder of the relation between procalcitonin and infection.^{30,33,34} In addition, lack of correction for reference ranges for neonatal procalcitonin values may also have influenced the outcome of procalcitonin as a marker for bacterial infection.^{27,30,33,34}

That results are contradictory is not surprising given the highly diverse groups of ill neonates with a mixture of diagnoses and conditions. Variations in study design, definition of infection, cut-off points of procalcitonin and CRP, and wide-ranging differences in postnatal age (hours to weeks) lead to difficulties in comparing studies. Procalcitonin may be a valuable marker for the detection of early neonatal infection when reference values, the clinical condition, and the administration of antibiotics are taken into account in both term and preterm neonates. Chiesa and colleagues¹⁸ studied all perinatal events and concluded that, compared with the increases in procalcitonin caused by these perinatal events, the magnitude of procalcitonin response to infection is much greater. Both the specificity

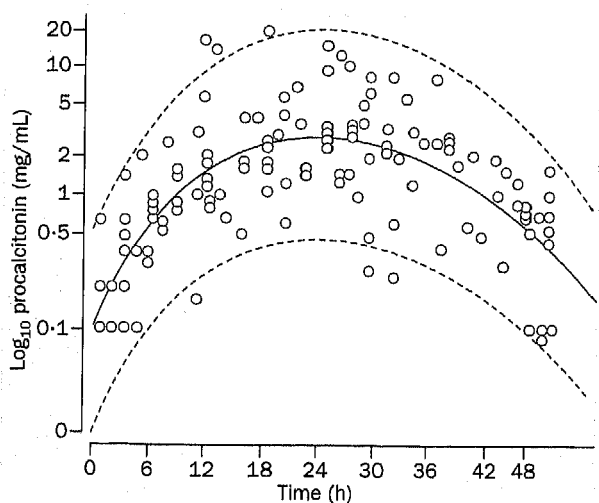


Figure 2. Age-specific 95% reference range for procalcitonin in healthy neonates ($n=83$) from birth to 48 h of life. Circles represent single values; dotted lines represent lower and upper limits; the bold line represents the geometric mean.¹⁹ Adapted with permission from Jaye and Waites.¹

Table 1. Neonatal infections

Study, year	Population	Number in study	Age	Gold standard	AUC ROC curves		Cut-off		Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)	
					CRP	PCT	CRP (mg/L)	PCT (ng/mL)	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT
Resch et al, ²³ 2003	Preterm and full-term suspected of infection	76	<12 h	Clinical signs of sepsis or increased risk for infection	2.5	2	69	83	96	61	96	76	67	70
					8	6	49	77	100	91	100	93	58	72		
					14	..	63	..	100	..	92	..	64	..		
Engle et al, ²⁴ 2003	Term neonates, respiratory symptoms >6 h postnatal	51	8–12 h and 48 h postnatal	Radiographic findings of pneumonia	0.61	0.75	1	1
Kordek et al, ²⁵ 2003	Preterm and full-term infected and non-infected	187	Umbilical cord	Clinical signs ± positive sepsis screen	0.61	0.75	2.5	1.2	22	69	97	81	20	42	86	93
Koskenvuo et al, ²⁶ 2003	Critically ill neonates	65	<12 h 72 h postnatal	Blood culture or clinical signs and positive sepsis screen
Chiesa et al, ¹⁸ 2003	Critically ill, preterm; infected and non-infected	219	Umbilical cord 24 h 48 h	Blood culture SNAP-PE37 ²⁸	0 h: 4	0 h: 1	74	79	83	95
					24 h: 10	24 h: 100	89	95	87	96		
					48 h: 10	48 h: 50	89	84	84	100		
Blommendahl et al, ²⁷ 2002	Preterm and full-term suspected of infection	169	Unknown	Blood culture	30	1	58	77	84	62	24	16	94	97
Guibourdenche et al, ²⁸ 2002	Preterm and full-term infected and non-infected	136	At birth	Blood/CSF culture ± clinical signs of sepsis ↑ or ↓ WBC	7.5	2.5	68	87	80	90	81	86	72	93
Athhan et al, ²⁹ 2002	Full-term infected vs full-term controls	34	Unknown	Tollner's scoring system ³⁹
Janota et al, ³⁰ 2001	Preterm infants (<1500 g and <31 weeks)	37	Umbilical cord +1 h, 48–72 h, and day 7 post natal	Blood culture or clinical signs and positive sepsis screen	1	2	25	75	90	75
Enguix et al, ³¹ 2001	Critically ill, term neonates; control group	20	3–30 days	Clinical + laboratory criteria ⁴⁰	0.95	0.99	23	6.1	96	99	84	89	80	90	97	99
		26	3–30 days	Blood culture
Silkora et al, ³² 2001	Preterm and full-term suspected of infection; control group	13	<12 h, 12–24 h after termination of antibiotic therapy	Blood culture or clinical signs and positive sepsis screen
		20
Bonac et al, ³³ 2000	Critically ill, preterm, and term neonates; control group	58	0–20 days	Blood culture or clinical signs and positive sepsis screen	0 h: 14	0 h: 10	36	59	92	82	43	36	89	92
		25	24 h: 29	24 h: 13	44	50	100	100	100	100	100	91	92	
		48 h: 12	48 h: 3	68	52	83	91	42	50	94	92		
Franz et al, ³⁴ 1999	Critically ill, preterm, and term neonates	162	0–11 days	Blood culture or clinical signs and positive sepsis screen	0 h: 10	0 h: 0.27	28	80	97	53	81	41	77	87
					12–36 h: 0.5	..	57	..	66	..	40	..	79	
Lapillonne et al, ³⁵ 1998	Critically ill, preterm and term neonates	150	0–10 days	Blood culture or clinical signs	5	30	84	..	91	..	56	..	77
					36–60 h: 3.5	..	30	..	50
Chiesa et al, ¹⁹ 1998	Critically ill	126	0–48 h and 3–30 days	Blood culture or clinical signs and positive sepsis screen	1	0.6	46	86

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Table 1. Neonatal infections (continued)

Study, year	Population	Number in study	Age	Gold standard	AUC ROC curves		Cut-off		Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)	
					CRP	PCT	CRP (mg/L)	PCT (ng/mL)	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT
Monneret et al, ⁴⁰ 1997	Critically ill, preterm, and term neonates; 49 control group	39	0–28 days	Blood/CSF/urine culture or two peripheral cultures with clinical signs of sepsis
Gendrel et al, ³⁶ 1996	Critically ill, preterm, and term neonates; 86 control group	68	0–15 days	Blood culture or clinical signs and positive sepsis screen	10

AUC ROC=area under the curve, receiver operating characteristic; CRP=C-reactive protein; CSF=cerebrospinal fluid; NPV=negative predictive value; PCT=procalcitonin; PPV=positive predictive value; SNAP-PE=score for neonatal acute physiology—perinatal extension; WBC=white blood cell count; ..=not available.

and sensitivity of procalcitonin were greater than those obtained for CRP.

Sepsis and meningitis

All studies on procalcitonin in children with sepsis, septic shock, or meningitis report that procalcitonin is an excellent marker of severe bacterial infection and that it has a diagnostic performance significantly greater than that of CRP concentration and leucocyte count (table 2). Sensitivity and specificity of procalcitonin varied from 83% to 100% and from 70% to 100%, respectively. For CRP, sensitivity and specificity were in a lower range (73–88% and 50–89%, respectively).^{31,43,46,47,51–53} The diagnostic value of procalcitonin was excellent, both for discriminating between viral and bacterial infections and between invasive and localised bacterial infections. Cut-off values differ widely between the studies, which can be a major practical problem when procalcitonin values are used in clinical practice. Most of the studies reported a cut-off value of 2 ng/mL as the best value for distinguishing between invasive and localised bacterial infections and between viral and bacterial infections.

Gendrel and colleagues⁵² found procalcitonin to be a better marker than CRP for distinguishing between bacterial and viral infections in children in the emergency room. They also found this for children who developed fever up to 12 h before presentation in the hospital. All patients with sepsis and meningitis had procalcitonin concentrations higher than the cut-off value of 0.6 ng/mL in the first analysis in the emergency department. In addition, the rapid semiquantitative test offered a better diagnostic performance than CRP, particularly in detecting invasive bacterial infections and in differentiating them from localised bacterial or viral infections. However, for the follow-up of procalcitonin concentrations and routine daily measurements, the quantitative luminometric assay is preferable.⁴³

Procalcitonin is also a useful indicator of the severity of bacterial infections. Three studies^{44,45,48} reported persistently increased procalcitonin concentrations associated with multiple organ failure and mortality in children with bacterial sepsis. However, Hatherill and colleagues⁴⁹ reported that a single procalcitonin measurement is an inadequate tool for prognosis and that serial procalcitonin

measurements might be of more value in the monitoring of the response to treatment in septic shock.

Procalcitonin is an excellent marker for severe, invasive bacterial infection in children. However, this test cannot be presented as the gold standard. The negative predictive value is not always 100%, and therefore a low procalcitonin value can falsely reassure physicians. However, it performs better than tests currently used (white blood cell count [WBC], CRP), and may be a useful adjunct in diagnosis.

Lower respiratory tract infections

Bacterial pneumonia cannot be differentiated from viral pneumonia on the basis of a patient's characteristics, routine laboratory tests, or chest radiographic findings.^{57–59} WBC or serum CRP concentration sometimes helps to differentiate between bacterial or viral causes. However, results of studies on the use of these markers have been inconsistent.^{60–62} Early indicators of cause and severity would help with the decision of whether to prescribe or to withhold antibiotics.

Only one study has been done among infants with bronchiolitis on procalcitonin and CRP values during the respiratory syncytial virus season.⁶³ This study showed that serum procalcitonin values were less than 0.5 ng/mL in 96% of the children with respiratory syncytial virus bronchiolitis without bacterial superinfection and that serum CRP values were less than 8 mg/L in 69% of these children.⁶³ Six studies have been published on the use of procalcitonin as a marker of bacterial causes of lower respiratory infection (table 3).^{63–69} Results of these studies are inconsistent. Three studies^{65,66,68} concluded that procalcitonin differentiates between bacterial infections and viral infections more effectively than CRP, WBC, or interleukin-6 in emergency department situations. However, another three studies^{64,67,69} stated that measurement of serum procalcitonin is of little value in differentiating between bacterial and viral pneumonia in children.

When assessing the usefulness of procalcitonin a few pitfalls have to be taken into account. First, results depend on the accuracy of the aetiological diagnosis of lower respiratory tract infection. Diagnosis of pneumococcal infection was based mainly on immune complex assays in paired sera or antigen assays in urine. These tests have thus far been used only for research purposes in specialised

Table 2. Sepsis and meningitis

Study, year	Population	Number in study	Age (years)	Aim of study*	Gold standard	AUC ROC curves		Cut-off (mg/L) (ng/mL)		Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)	
						CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT
Fernandez Lopez et al, ⁴³ 2003	Fever requiring hospital admission	445	0.08–3	1	Positive culture in blood/CSF	0.81	0.95	27.6	0.59	78	91	75	94	69	91	81	90
Casado-Flores et al, ⁴⁴ 2003	Admission to PICU due to sepsis	80	0.08–16	2	Clinical+ laboratory criteria ⁴⁴
Han et al, ⁴⁵ 2003	Sepsis or septic shock; critically ill controls without sepsis	78 12	4–8	1, 2	Clinical+ laboratory criteria (sepsis, ⁴⁵ septic shock ⁴⁶)
Prat et al, ⁴⁶ 2003	Fever <12 h; bacterial sepsis/ meningitis; aseptic meningitis; localised bacterial infection; controls	25 18 22 25	0.08–12	1	Positive culture in blood/CSF	0.85	1	40	2	88	100	50	100	64	100	91	100
Carrol et al, ⁴⁷ 2002	Fever+purpuric rash	108	0.07–15.9	3	Positive blood culture	0.90	0.96	30	2	81	94	89	93	91	95	76	91
Van der Kaay et al, ⁴⁸ 2002	Meningococcal sepsis±septic shock	64	0.77–12.4	3	Severity, survivors vs non-survivors	0.42	0.79
Enguix et al, ⁴⁹ 2001	Critically ill; controls	52 64	2–12	2	Clinical+ laboratory criteria ⁴⁹	0.93	1	22	8	89	100	81	100	80	100	89	100
Hatherill et al, ⁴⁹ 2000	Septic shock	75	0–16	3	Clinical+ laboratory criteria ⁴⁴
Somech et al, ⁵⁰ 2000	Unexplained fever/sepsis examination	38	0.3–11	3	None
Hatherill et al, ⁵¹ 1999	Admission to PICU	175	0.1–16.1	1	Positive bacteria isolate	0.83	0.96†	50†	20†	76†	83†	80†	92†	76†	90†	80†	87†
Gendrel et al, ⁵² 1999	Hospital admission for fever >38.5°C, known pathogen	360	0.3–15	1	Positive bacterial or viral isolate	0.89	0.94§	40§	1§	73§	83§	88§	93§	76§	86§	86§	91§
Gendrel et al, ⁵³ 1997	Hospital admission for meningitis	59	0.4–13	1	Positive bacterial or viral CSF culture	5	..	94	..	100
Assicot et al, ³ 1993	Hospital admission for severe infection	79	0–10	1	Positive bacterial or viral isolate

*The aim of the study was to: 1=use procalcitonin (PCT) as a diagnostic marker of severe bacterial infection; 2=use procalcitonin as a prognostic marker of sepsis/multiple organ failure; 3=determine correlation between C-reactive protein (CRP) and PCT. †All values for septic shock only; ‡All values for children with septic shock and/or bacterial meningitis; §To distinguish between invasive or localised bacterial infections and viral infections; ¶To distinguish between invasive bacterial infections and localised bacterial or viral infections. AUC ROC=area under the curve, receiver operating characteristic; CSF=cerebrospinal fluid; NPV=negative predictive value; PPV=positive predictive value; PICU=paediatric intensive care unit; ..=not available.

laboratories, and their clinical value has not been established.^{61,70} Prat and colleagues⁶⁵ analysed differences between pneumococcal pneumonia diagnosed by blood cultures and by urinary antigen and found no differences in WBC, CRP, or procalcitonin. This suggests that a pneumococcal pneumonia diagnosed by urinary antigen is as reliable as pneumococcal pneumonia diagnosed by blood culture.⁶⁵ In some children, pneumococcal infection was

diagnosed only by immune complexes.⁶⁴ These children may have had another localised infection with *Streptococcus pneumoniae*—for example, otitis media—without true bacterial pneumonia. Second, the use of antibiotics before enrolment to the study or before the measurement of procalcitonin could be a major confounding factor. Procalcitonin concentration decreases rapidly if the bacterial infection is treated, reaching normal values within 1 or 2

Table 3. Respiratory infections

Study, year	Population	Number in study	Age (years)	Aim of study*	Gold standard	AUC ROC curves		Cut-off (mg/L) (ng/mL)		Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)	
						CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT
Korppi et al, ⁶⁴ 2003	Radiologically confirmed CAP	190	0-15	1	Chest radiograph, positive bacterial/atypical/viral isolates	..	0.58	60	0.5	..	46	..	52	..	65
Resch et al, ⁶⁵ 2003	Infants admitted to hospital with bronchiolitis	48	0.04-1	2	Rapid RSV test on nasopharyngeal aspirate; bacterial blood culture
Prat et al, ⁶⁶ 2003	ER clinical signs of lower RTI	85	0.5-10	3, 4	Blood cultures, nasopharyngeal aspirate for viral studies	0.78	0.76	65	2	79	69	67	79
Hatzistilianou et al, ⁶⁶ 2002	Hospital admission for clinical signs of lower RTI	73	2-14	4	Chest radiograph, positive bacterial/atypical/viral isolates	2	2	96	100	38	98	42	93
Korppi et al, ⁶⁷ 2001	Hospital admission for clinical signs of lower RTI	58	3 (mean)	5	Chest radiograph, positive bacterial/atypical/viral isolates	..	0.61	..	0.5	..	55	..	71
Moulin et al, ⁶⁸ 2001	Hospital admission for clinical signs of lower RTI	72	0.2-13	4	Positive bacterial/atypical/viral isolates, seroconversion	0.84	0.93	20	0.5	88	95	40	80	72	80	67	88
Toikka et al, ⁶⁹ 2000	Hospital admission for clinical signs of lower RTI	126	0.1-17	3, 5	Positive bacterial/atypical/viral isolates, seroconversion	80	2	59	50	68	80
								150	7	31	19	88	98

*To use procalcitonin (PCT) to differentiate between: 1=viral and bacterial causes of community acquired pneumonia (CAP) in the primary healthcare setting; 2=viral and bacterial causes of bronchiolitis; 3=viral and bacterial or atypical causes of CAP; 4=viral or atypical and bacterial causes of CAP; 5=viral and bacterial or mixed causes of CAP. AUC ROC=area under the curve, receiver operating characteristic; CRP=C-reactive protein; ER=emergency room; NPV=negative predictive value; PPV=positive predictive value; RSV=respiratory syncytial virus; RTI=respiratory tract infection; ..=not available.

Table 4. Urinary tract infections

Study, year	Population	Number in study	Age (years)	Aim of study*	Gold standard	AUC ROC curves		Cut-off (mg/L) (ng/mL)		Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)	
						CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT
Prat et al, ⁷⁸ 2003	ER clinical signs of UTI and abnormal urinalysis	77	0.1-12	1	Positive urine culture; DMSA scan for renal scarring	0.72	0.83	20	1	62	92	34	92	23	32	95	98
Smolkin et al, ⁷⁹ 2002	ER clinical signs of UTI and abnormal urinalysis	64	0-3	2	Positive urine culture; DMSA scan for renal involvement	20	0.5	100	94	19	90	31	86	100	98
Gervais et al, ⁸⁰ 2001	ER clinical signs of UTI and abnormal urinalysis	54	0-16	2, 3	Positive urine culture; DMSA scan for renal involvement	40	0.5†	68	74	55	85
Benador et al, ⁸¹ 1998	ER clinical signs of UTI and abnormal urinalysis	80	0.1-16	1, 2	Positive urine culture; DMSA scan for renal involvement	10	0.6	100	70	26	83

*Aim of study was to: 1=use procalcitonin (PCT) as a discriminator between uncomplicated urinary tract infection (UTI) and severe acute pyelonephritis with renal scarring; 2=use PCT as a discriminator between uncomplicated UTI and severe acute pyelonephritis; 3=determine the correlation between the quantitative (LUMitest PCT, Brahms Diagnostica) and the rapid semi-quantitative PCT test (Brahms PCT-Q, Brahms Diagnostica). †Brahms PCT-Q test was used. AUC ROC=area under the curve, receiver operating characteristic; CRP=C-reactive protein; DMSA=^{99m}Tc-dimercaptosuccinic acid; ER=emergency room; NPV=negative predictive value; PPV=positive predictive value; ..=not available.

Table 5. Fever without localising signs

Study, year	Population	Number In study	Age (years)	Aim of study	Gold standard	AUC ROC curves		Cut-off (mg/L) (ng/mL)		Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)	
						CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT
Galetto-Lacour et al, ⁶⁸ 2003	Fever >38°C and no localising signs of infection	99	0-02-3	CRP/PCT culture as a discriminator for severe bacterial infections	Blood/CSF, urinary culture+DMSA defects; chest radiograph	40	0.5	79	93	79	74	90	96	61	61
Galetto-Lacour et al, ⁶⁹ 2001	Fever >38°C and no localising signs of infection	124	0-02-3	CRP/PCT as a discriminator for severe bacterial infections	Blood/CSF/culture, urinary culture+DMSA defects; chest radiograph	40	0.9	89	93	75	78	96	97	51	55

AUC ROC=area under the curve, receiver operating characteristic; CRP=C-reactive protein; CSF=cerebrospinal fluid; DMSA=^{99m}Tc-dimercaptosuccinic acid; ER=emergency room; NPV=negative predictive value; PCT=procalcitonin; PPV=positive predictive value; ..=not available.

days, whereas CRP concentrations can increase during the first few days of antibiotic treatment.^{4,5} Toikka and colleagues⁶⁹ found a marked overlap of procalcitonin and CRP within bacterial and viral causes. They hypothesised that some bacterial pneumonias are mild with only minor changes on the chest radiograph and with a modest host inflammatory response, and that some of the viral pneumonias are severe with major changes on the chest radiograph and in the host response.⁶⁹

It is currently not possible to determine whether a patient should be given antibiotics solely on the basis of procalcitonin concentration, but high values indicate the presence of bacterial infection. Further studies with an adequate definition of bacterial lower respiratory infection, and without pretreatment with antibiotics, should be done.

Urinary tract infections

The diagnosis of UTI is often not straightforward in paediatric practice. Infection of the lower tract is more likely to spread to the upper tract and kidneys in children than in adults.⁷¹⁻⁷³ The non-specific nature of signs and symptoms in febrile infants and children makes the clinical differentiation between acute pyelonephritis and lower UTI difficult. Acute pyelonephritis should be distinguished from lower UTI because it can lead to chronic renal damage and, in the event of extensive renal scarring, can lead to arterial hypertension and renal insufficiency.⁷⁴

^{99m}Tc-dimercaptosuccinic acid (DMSA) is an isotope-labelled substrate that is absorbed in the proximal tubules. Its renal uptake can be measured and affected areas are seen as uptake defects. This test is considered the gold standard for the diagnosis of acute pyelonephritis when done in the

Table 6. Fever in paediatric oncology

Study, year	Population	Number In study	Age (years)	Aim of study*	Gold standard	AUC ROC curves		Cut-off (mg/L) (ng/mL)		Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)	
						CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT
Sauer et al ⁶⁶ 2003	Bone-marrow -transplant recipients	47	1-27	1, 2, 3	ACCP-SCCM definition ⁶¹	50	1	100	56	41	87	46	69	100	80
Barnes et al, ⁶⁹ 2002	Febrile neutropenia	4	Duration of admission >5 days	0.2	..	80	..	35	83
Flieschhack et al, ⁶⁸ 2000	Febrile neutropenia	51	0.7-31.8	5, 6	Positive culture of urine, faeces, throat swabs, bronchoalveolar lavage± clinical signs	Prediction of Gram-negative bacteraemia	10	0.3	100	80	21	44
	Control group	35	1.2-28.8			Prediction of fever of unknown origin	10	0.3	14	64	81	69
						of unknown origin	50	0.5	76	95	39	35
						of unknown origin	100	1.0	96	100	10	15
						of unknown origin	5.0	5.0	..	100	..	9
de Bont et al, ⁶⁹ 2000	Febrile neutropenia	49	..	6	ACCP-SCCM definition ⁶¹	0.5	94	28	40	79	38	33	95	75

*Aim of study was: 1=to compare serum levels of procalcitonin (PCT) and C-reactive protein (CRP) during sepsis; 2=to determine predictive value of PCT for the outcome of sepsis; 3=to determine correlation between PCT and severity of sepsis; 4=to determine predictive value of PCT on length of admission; 5=to use PCT to monitor the response to antibiotic therapy; 6=to determine predictive value of PCT for severe systemic infection. ACCP-SCCM=American College of Chest Physicians-Society of Critical Care Medicine; AUC ROC=area under the curve, receiver operating characteristic; NPV=negative predictive value; PPV=positive predictive value; ..=not available.

acute phase and for the diagnosis of renal scarring secondary to pyelonephritis 5–6 months after the infection episode.^{72,75–77} However, DMSA scintigraphy is an expensive investigation that is not readily accessible in all centres. It also exposes the patient to radiation, and does not differentiate between old scarring and acute parenchymal involvement unless a follow-up scan is done.

Procalcitonin and CRP were assessed as tests that could possibly distinguish lower UTI from acute pyelonephritis at the time of diagnosis (table 4).^{78–81} Benador and colleagues⁸¹ noted a 100% sensitivity of CRP. Thus, all children with normal CRP values could be safely considered not to have acute pyelonephritis and would not require either DMSA scans or early parenteral antibiotic therapy. However, the low specificity (26.1%) limits its clinical usefulness and leads to unnecessary hospital admissions. The specificity of procalcitonin (82.6%) was found to be much higher than that of CRP. The sensitivity of an increase in procalcitonin was 70.3%, and 11 children were found with very mild (defect covering <5% surface area) or mild lesions (defect covering 5–10% surface area) with a normal procalcitonin value. Thus, procalcitonin alone cannot be used to identify all renal lesions because 30% of patients had normal procalcitonin concentrations despite grade 1 and 2 lesions. However, procalcitonin is found to correlate with the severity of renal lesions at time of diagnosis, and possibly with the risk of permanent scarring. Prat and colleagues⁷⁸ reported a significant correlation between high procalcitonin values at the time of admission and renal damage. In addition, they found that procalcitonin yields a high negative predictive value of renal damage, meaning that a low procalcitonin value at the time of admission, despite clinical signs of pyelonephritis, points to a low risk of renal scarring. These results are in accordance with the other three studies that were done.^{79–81}

Gervaix and colleagues⁸⁰ examined the correlation between the quantitative and the rapid semiquantitative test. The blood samples tested with both methods showed a good correlation. No result above 0.5 ng/mL with the quantitative method was below the threshold of detection (0.5 ng/mL) of the rapid test.

In conclusion, the data indicate that the procalcitonin test on admission has a high sensitivity and specificity for differentiating between acute pyelonephritis and lower UTI in infants and children, when compared with the low specificity of CRP or WBC. Procalcitonin measurement might therefore be a useful and practical tool for the diagnosis of acute pyelonephritis in infants and children, and allow informed decisions to be made about parenteral or oral antibiotic treatment in these patients. The use of the rapid semiquantitative test needs further evaluation.

Fever without localising signs

Fever without localising signs in young children is a difficult diagnostic problem, since clinical signs and symptoms are often unreliable predictors of a serious bacterial infection. Although most of these children have benign, self-limiting diseases, a few are at risk of developing a severe bacterial infection, which requires administration of parenteral

antibiotics. Galetto-Lacour and colleagues⁸² reported the results of procalcitonin used in children with fever without localising signs (table 5). Children treated with antibiotics during the preceding 2 days were excluded. Procalcitonin and CRP resulted in a similar sensitivity and specificity for predicting serious bacterial infection (bacteraemia, pyelonephritis, lobar pneumonia, and meningitis). A severe bacterial infection was diagnosed in 23% of the children (n=28: four bacteraemia, 19 pyelonephritis, five lobar pneumonia). A higher sensitivity and specificity for procalcitonin than for CRP has previously been reported by the same group in children with pyelonephritis.⁸⁰ Given the high number of children with pyelonephritis in this group of children with fever without localising signs, it is surprising that this study results in equal sensitivity and specificity for CRP and procalcitonin. The diagnosis of pneumonia was based on chest radiography, which has been shown not to be discriminative between viral and bacterial causes. Therefore, these children could have had a viral pneumonia, which might result in a lower specificity of procalcitonin in this study.⁵⁸ Galetto-Lacour and colleagues⁸³ reported a similar study which used the rapid semiquantitative test. This study, in which 29% of the children were diagnosed with a severe bacterial infection (n=29: four bacteraemia, 21 pyelonephritis, two lobar pneumonia, one mastoiditis, one retropharyngeal abscess), showed the same results as their previous study.⁸² Further studies with an adequate definition of severe bacterial infection are needed to determine the value of procalcitonin as a marker for fever without localising signs in children.

Fever in paediatric oncology

In neutropenic cancer patients, early markers are needed that are regulated or released independently of the leucocyte count and of the activity of the underlying disease. Studies in adults have shown that immunocompromised patients are capable of producing high serum concentrations of procalcitonin during severe systemic bacterial or fungal infections.^{84,85} Fleischhack and colleagues⁸⁶ showed that the activity of the underlying malignant disease, the chemotherapy-induced tissue damage, and the severity of neutropenia did not cause substantial increases in plasma concentrations of procalcitonin. In another study, they concluded that the overall diagnostic efficiency of procalcitonin was superior to that of CRP in the early detection of Gram-negative bacteraemia in fever without localising signs.⁸⁷ However, both sensitivity and specificity are low compared with other studies on the use of procalcitonin in children with sepsis.^{31,43,46,47} Sauer and colleagues⁸⁸ reported that serum procalcitonin correlates with the severity of sepsis in paediatric recipients of bone-marrow transplants who are profoundly immunocompromised, and that it may reliably identify children with a high mortality risk. The use of procalcitonin in febrile neutropenic children has to be established in future studies, but with a high specificity for Gram-negative bacteraemia (97–99%) a low procalcitonin concentration is reassuring for the physician. Table 6 summarises studies on the use of procalcitonin in paediatric oncology.

Discussion

Procalcitonin is an excellent marker of severe, invasive bacterial infection in children. All studies on severe, invasive bacterial infections in children report higher sensitivities and specificities of procalcitonin than for CRP.^{31,43,46,47,51,52} However, the use of procalcitonin as a marker of neonatal bacterial infection is complicated by several factors, and procalcitonin cannot be presented as the gold standard. The negative predictive value is not always 100%, and therefore a low procalcitonin value may falsely reassure physicians. However, procalcitonin performs better than other tests currently used (WBC, CRP), and may be a useful adjunct in diagnosis.

The use of procalcitonin in the diagnosis of neonatal bacterial infection is also complicated. First, infants with respiratory distress syndrome, haemodynamic failure, perinatal asphyxia, intracranial haemorrhage, pneumothorax, or after resuscitation have raised serum procalcitonin concentrations that do not differ from those of septic neonates up to 48 h after onset of clinical signs of distress or infection.^{20,33,35} Second, a physiological increase of procalcitonin has been reported up to 48 h post partum.¹⁸⁻²¹ Third, prepartum and intrapartum administration of antibiotics may affect procalcitonin concentrations in the umbilical cord,⁴² and postnatal administration of antibiotics will decrease procalcitonin concentrations more rapidly than CRP concentrations.^{4,5} Despite these pitfalls, procalcitonin performs better than CRP in diagnosing neonatal bacterial infection. All studies in neonates report a higher sensitivity for procalcitonin than for CRP.^{18,19,23,25,27,28,30,31,33,34} Most studies report a lower specificity for procalcitonin than for CRP.^{23,27,30,33,34} However, many of these studies did not consider the higher age-specific reference ranges for neonates that could explain the lower specificities for procalcitonin.^{27,30,33,34} Studies that corrected for age-specific reference ranges resulted in a higher specificity of procalcitonin than of CRP.^{18,28,31}

When a severe bacterial infection is suspected, high sensitivity of a test might be more important than high specificity to avoid making a false-negative diagnosis. However, for diseases that are not life threatening, a high specificity rather than a high sensitivity may be more preferable to avoid unnecessary hospital admissions and the unnecessary use of antibiotics. In all studies on the use of procalcitonin for diagnosing a bacterial cause of lower respiratory tract infection and acute pyelonephritis, procalcitonin has a high specificity, which was higher than the specificity of serum CRP concentrations.^{65,66,68,69,78-81} Most studies reported high sensitivities of both serum procalcitonin and CRP.^{65,66,68,78-81} In half of the studies, a higher sensitivity for CRP was found,^{1,65,69,79,81} whereas in the other half the sensitivity of procalcitonin was higher.^{66,68,78,80}

The use of procalcitonin as an early marker of bacterial infection in children with febrile neutropenia or fever without localising signs has to be established, since only a few, contradictory studies have been done.^{80,83-87} The use of a combination of serum procalcitonin and CRP did not lead to a better sensitivity or specificity in these children. In addition, studies on children with neonatal sepsis, pneumonia, or UTIs did not show that a combination of CRP and procalcitonin improved the sensitivity or specificity.^{28,69,81,82}

Interpretation of the literature on the use of procalcitonin as an early marker of bacterial infection is complicated by the variation in cut-off values and by diverse study populations. Heterogeneity not only within the study group, but also within categories defined as "sepsis", "distress", "infected", "respiratory distress", or even "haemodynamic failure" is huge. Future studies will need to use rigidly defined categories of infection in homogeneous populations to get results that can be clearly interpreted and compared. The finding of a single cut-off value will remain a problem since a zone of uncertainty will always exist. For use in neonates, age-specific reference values, underlying disease, and maternal use of antibiotics should be taken into account. In sepsis, most studies report an optimum cut-off value of 2 ng/mL procalcitonin. In children with respiratory infections, the optimum cut-off value varies between 0.5 and 2 ng/mL, and in children with UTIs between 0.5 and 1 ng/mL. The rapid semiquantitative test offered better diagnostic performance than CRP in severe, invasive infections, and in UTIs.^{43,46,78} Gervais and colleagues⁸⁰ observed an excellent correlation between the quantitative and the rapid semiquantitative test.

In light of the favourable results of all studies on the use of procalcitonin as an early marker of bacterial infection in neonates and children, we find it surprising that the use of CRP in clinical practice has not been displaced by the use of procalcitonin. In addition to the high sensitivity and specificity, procalcitonin has other advantages in clinical practice. The rapid kinetics result in an increase of procalcitonin within 6-8 h of the onset of fever, reaching a plateau within 12 h, and a rapid decrease after the administration of antibiotics.⁵ In addition, procalcitonin has been shown to correlate with severity of disease, and could therefore be used as a prognostic marker.^{44,45,48,78} The widespread use of procalcitonin as a marker might be prohibited by the higher costs of procalcitonin tests compared with the costs of CRP tests. However, cost-effectiveness studies have not yet been done. The high specificity of

Search strategy and selection criteria

Data for this review were identified by searching for articles on procalcitonin as a marker for bacterial infection in neonates, infants, and children in the PubMed database up to December 31, 2003. We searched only for papers in English. Review articles and comments on previously published articles were excluded. Search terms were "procalcitonin" in combination with "neonatal", "neonates", "infants", "children", "pediatric", and "paediatric". 18, 45, 23, 53, 19, and seven articles, respectively, were available. Of these 165 articles, 74 were duplicates. After also excluding articles not written in English (n=17), review articles (n=9), case reports (n=1), and comments on previously published articles (n=6), the abstracts of the remaining 58 articles were read to determine whether the subject of the article was "procalcitonin as early marker for bacterial infection in neonates or children". 12 articles were excluded after reading, because the subject was not procalcitonin as an early marker for bacterial infection in neonates or children. Bibliographies of all included articles were checked for additional publications and did not reveal more articles. 46 original articles were available for this review.

procalcitonin might reduce the use of antibiotics and hospital admissions. Recently, Christ-Crain and colleagues⁹² showed that the use of procalcitonin in adults with infections of the lower respiratory tract halves antibiotic use without altering the clinical outcome. The characteristics of procalcitonin could therefore result in a favourable cost-effectiveness of procalcitonin versus CRP, despite the higher costs of the determination of procalcitonin concentrations.

In conclusion, the use of procalcitonin as an early marker of bacterial infection in neonates, infants, and children results in better overall sensitivity and specificity than CRP, and is a valuable additional tool for the diagnosis of bacterial disease in this group of patients.

Conflicts of interest

The authors have no conflict of interest with respect to the contents of this paper. There was no funding for this paper.

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