Is Procalcitonin Useful in Pediatric Critical Care Patients?

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ABSTRACT: This review examines the use of procalcitonin in different clinical situations in the pediatric patient, with special emphasis on those requiring intensive care. We review the latest articles on its potency as a biomarker in both infectious processes at diagnosis and on the response to treatment.

KEYWORDS: PCT, infections, PICU, stewarship, biomarker

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Introduction

Infections are one of the most prevalent pathologies in pediatric intensive care units (PICU). In fact, invasive bacterial infection (IBI) is a major cause of morbidity and mortality in adult and pediatric populations, affecting up to 20% to 70% of hospitalized cases.[1,2] Patients with severe infection may develop an systemic inflammatory response syndrome (SIRS)[3] which, in fact, has been part of the diagnosis criteria of septic patients.[4] The differential diagnosis between IBI and viral infection is not always easy, especially in younger patients. What's more, SIRS may occur in other pathologies besides IBI,[5] as happens post-surgery[6,7] and in polytrauma patients.[8]

Another important issue related to IBI is that the correct control of the infection requires an early specific diagnosis,[9–11] both in adults and in pediatric patients. Some analytical data such as leukocyte count, immature white cell count,[12] and C-reactive protein value (CRP)[13,14] have been classically used to distinguish between bacterial and viral infection, but they are unspecific.[15] A correct approach to IBI management focuses on individualized and appropriate duration of the antibiotic treatment, to prevent antibiotic resistance and improve the prognosis. During the past 15 years, different publications have reported the use of procalcitonin (PCT) to help at different points in the approach to IBI—in diagnosis, monitoring, and prognosis—and as a guide to the duration of antibiotic treatment.[16,17]

The aim of this review was to determine whether PCT might be a useful marker in critically ill pediatric patients with IBI. For the present review, articles published up to January 2018 were reviewed. The search was performed in PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials. In this review, studies of the adult population have been included due to the lack of data in pediatric patients in some situations.

What Is Procalcitonin?

Procalcitonin is a 116 peptide of 13-kDa amino acid, without any hormonal activity, and a precursor of calcitonin hormone. Routinely produced in the C cells of thyroid gland, PCT reaches the bloodstream where levels below ng/mL may be detected.[18] However, in 1993, the behavior of PCT in the context of sepsis was described[19] and its use as a biomarker became widespread in the last 10 years.[20–22] Procalcitonin increases after exposure to endotoxins,[23] which makes it more or less specific for bacterial infections, depending on the invasiveness of the pathogen. In addition, the cytokines released in viral infections appear to attenuate PCT levels.[24,25]

A biomarker is an indicator of a normal or pathological biological process. It can be analyzed in different biological liquids. A good biomarker allows for the diagnosis of the disease, determination of its severity, follow-up on its evolution, and evaluation of a response to treatment.[26] Procalcitonin is a biomarker that meets many of these requirements, especially in infectious processes, both for early diagnosis and to monitor antimicrobial treatment. Bacterial infection induces the expression of the PCT gene (calcitonin gene-related peptide 1 [*CALC-1*]) in different organs, raising PCT levels.[18,27] In healthy volunteers, it is detected at 4 hours after an *Escherichia coli* endotoxin infusion, with a plateau at between 8 and 24 hours, and a mean life of 24 to 36 hours.[23] It is minimally dependent on renal function. The utility of PCT has been documented in different clinical situations that will be discussed in separate points.

Procalcitonin and Bacterial Infection Diagnosis

Procalcitonin and infection

Procalcitonin seems to have better Sensitivity (Sn) and Specificity (Sp) than CRP for IBI diagnosis. The multicenter study by Lopez et al[28] showed that in an emergency department, PCT allowed an early IBI diagnosis in febrile infants (under 36 months), with better cutoffs than CRP: PCT 0.69 ng/mL (Sn 85.7%; Sp 98.5%) and for CRP, 19 mg/L (Sn, 61.3%; Sp, 80%). The authors considered IBI in the following infectious diseases confirmed by specific cultures: meningitis infections, sepsis, bone or joint infections (local isolation or in blood culture of the microorganism), acute pyelonephritis infections, lobar pneumonia, bacterial enteritis in infants under 3 months, and occult bacteremia.

In sepsis cases, Rey et al[29] demonstrated similar results, with a better diagnosis area under the curve (AUC) for PCT (0.91; 95% confidence interval [CI], 0.882-0.943) than for CRP (0.75; 95% CI, 0.699-0.802) in sepsis. Another important factor suggested by Rey was the possibility of classifying patients according to severity using PCT: the higher the value of PCT, the greater the severity of sepsis. Procalcitonin values more than 24.5 ng/mL were present in septic shock, values between 1.16 and 9.33 ng/mL corresponded to both sepsis and SIRS, and values below 0.89 ng/mL were rarely present in septic patients. Another important factor suggested by Rey was the possibility of classifying patients according to severity using PCT.

Fever without source (FWS) is a major problem in young infants in an emergency department. Luaces-Cubells et al[30] reported that PCT was the most useful biomarker to predict IBI in infants with FWS, even in rapidly evolving cases with fever duration of less than 8 hours, establishing the optimum cutoff for PCT: 0.9 ng/mL (Sn 86.7%, Sp 90.5%) and the optimum cutoff for CRP 91 mg/L (Sn 33.3%, Sp 95.6%). There are other publications with similar results.[31–33] Moreover, whereas PCT increases in severe bacterial infections, the levels remain low (<1 ng/mL) in common viral infections.[34] Interestingly, PCT can be introduced in models to explain the differing evolution of sepsis such as the PIRO concept: predisposing, infection, response, and organism.[35] It would appear as a patient response part. In the same way, it is included in the sepsis guidelines, as a criterion of the SIRS definition, with abnormal results up to 2 standard deviations from normal values.[36,37] To decide on patient transfer from the ICU to the general ward, PCT seems to be useful too.[16] All data from the pediatric studies regarding the usefulness of PCT in fever with unknown focus or invasive infections are summarized in Table 1.

Other studies have determined that PCT levels increase in other causes of bacterial infection. Although not all of them compared PCT with other biomarkers or gold standards, results on the usefulness of PCT appear to be promising, and they are detailed below in subsections.

- Urinary tract infections

Another use of PCT in febrile patients is the differential diagnosis of lower urinary tract infection and pyelonephritis, with an upper cutoff point of 0.5 to 1 ng/mL.[41–44] In a more recent meta-analysis, levels > 0.5 ng/mL predict the presence of renal parenchymal involvement. Therefore, PCT has been included in a clinical practice guideline.[45] Table 2 summarizes the main studies to analyze the use of PCT in urinary tract infections.

- Respiratory infections

An important indication of PCT is in suspected pneumonia, especially in pediatric patients in whom viral infections are clinically similar to bacterial infections, when radiology and other laboratory data do not increase diagnostic accuracy.[46] There are no recent studies in this area in pediatrics (Table 3). In the Toikka et al[46] study, the median PCT value in bacterial pneumonia was 2.09 ng/mL vs 0.56 ng/mL in viral pneumonia ($P = .019$). Therefore, PCT levels >2 ng/mL could suggest bacterial pneumonia but it has to be noted that cases with normal values of short evolution should be monitored.[49,50] Lower values of PCT do not permit one to distinguish between bacterial and viral pneumonia.[47,48] Furthermore, PCT does not allow us to distinguish between viral infection and infection with *Mycoplasma pneumoniae* or *Chlamydia pneumonia*[51] nor has it been proven to reduce the duration of antibiotic treatment in adults.[52]

- Neonatal infections

Neonates present a physiological induction of an acute inflammatory reaction in the peripartum.[53,54] Therefore, there is some difficulty in interpreting the PCT values in this situation to make a diagnosis of infection. In addition, some reports have detected elevated PCT levels in newborns with respiratory distress syndrome in the absence of any other signs of infection.[55,56] There are even studies in which PCT is analyzed in umbilical cord blood for the diagnosis of early onset sepsis,[57] although this use has not been extended to neonatal units. There are modified charts for this situation that help with the diagnosis and interpretation of PCT in the neonatal patient, along with clinical judgment.[58–60] In addition, a repeated measurement of PCT can be performed and if there is a progressive increase in its levels, an infectious complication should be suspected. From the third day of life in small infants, PCT values should be the same as those discussed in pediatrics and in adults and older children.[58] So PCT could lead to reduced antibiotic therapy duration.[54] A number of studies performed in newborns are summarized in Table 4. Interestingly, Hahn et al[68] reported that reference levels in low premature newborns with gestational age <32 weeks were different according to postnatal age: higher in those with lower gestational age or with fewer days. This must be considered.

Table 1. PCT to discriminate invasive infections, fever of unknown origin.

STUDY	TYPE	POPULATION	N	AGE	AIM	GOLD STANDARD	AUC	CUTOFF[a]	SN (%)	SP (%)	PPV (%)	NPV (%)	CONCLUSIONS
Mahajan (2014)[32]	P, M	ED, febrile fever of unknown origin	226 SBI 30	<36 mo	PCT compared with traditional screening tests for detecting SBI	CRX, cultures	0.80	0.6	51	93	13	86	SBI = bacteremia, urinary tract infections, bacterial meningitis, lobar pneumonia, or bacterial enteritis. PCT is accurate for identifying young febrile infants and children with serious SBIs.
Luaces-Cubells (2012)[30]	P, M	ED, febrile and non-toxic appearance	868 IBI 15	1-36 mo	PCT for IBI	CRX, cultures	0.87	0.9	86.7	90.5	—	—	IBI = meningitis, bacteriemia oculta or sepsis. PCT as a useful biomarker to predict IBI in non-toxic-appearing children less than 3 years of age with fever without apparent focus and absence of leukocytes in urine.
Rey (2007)[29]	P	PICU, all patients admitted	94	0-14 y	PCT for detecting sepsis and to stratify according to severity	CRX, cultures	0.91	1.16	92	76	—	—	PCT is a better diagnostic marker of sepsis in critically ill children than CRP.
Lopez et al (2003)[28]	P, M	ED, febrile children	445 IBI 150	1-36 mo	PCT for distinguishing viral and bacterial infection and for early diagnosis of IBI	CRX, cultures microbial tests, DMSA	0.95	0.59	91	94	90.8	90.1	PCT offers better E than CRP for differentiating viral and bacterial cause of the fever and offers better Sn and Sp than CRP to differentiate IBI.
Gendrel (1999)[34]	P	ED. Hospital admission for fever	360 IBI 46	1 mo-15 y	PCT for distinguishing viral and bacterial infection	Microbial test and cultures	0.94	1	83	93	86	91	PCT was a better marker than CRP, IL-6, or IFN-alpha for distinguishing between bacterial and viral infections in children in the ED. PCT is a useful indicator of the severity of IBI
Chakravarti (2016)[79]	R	CICU Infection suspected after CS	98	0-21 y	PCT to distinguish between the presence or absence of IBI	CRX, cultures	0.74	2	81.8	66.7	23.7	96.7	All included patients were suspected of infection. PCT levels were higher in the confirmed IBI
Bobillo (2016)[81]	P	NICU, after CS	51	<1 mo	Kinetics of PCT and its usefulness for diagnosis IBI	Clinical examination, CRX, cultures	0.87	5	87.5	72.6	29	97.8	No differences in PCT after CS with CPB and non-CPB. PCT could determine the absence of sepsis at 24 h after CS
Garcia (2012)[39]	P	PICU, after CPB in CS	231	1 mo-16 y	PCT to distinguish between SIRS and postsurgical infection after CPB	Clinical examination, CRX, cultures	0.86 (48 h)	4	62	87.9	61.5	—	PCT after CPB is useful in the diagnosis of IBI. Values above the limit for each period should alert IBI to initiate or modify antibiotic treatment.

Abbreviations: AUC, area under the curve; CAP, community acquired pneumonia; CICU, cardiac intensive care unit; CPB, cardiopulmonary bypass; CRP, C-reactive protein; CRX, chest x-ray; CS, cardiothoracic surgery; DMSA, ^{99m}Tc-dimercaptosuccinic acid; ED, emergency department; IBI, invasive bacterial infection; IFN, interferon; IL-6, interleukin 6; M, multicenter study; NICU, neonatal intensive care unit; NPV, negative predictive value; P, prospective study; PCT, procalcitonin; PICU, pediatric intensive care unit; PPV, positive predictive value; R, retrospective study; SBI, serious bacterial infection; SIRS, systemic inflammatory response syndrome; Sn, sensitivity; Sp, specificity.

[a]Cutoff value for procalcitonin. Values expressed in ng/mL.

Table 2. PCT in urinary tract infections.

STUDY	TYPE	POPULATION	N	AGE	AIM	GOLD STANDARD	AUC	CUTOFF[a]	SN (%)	SP (%)	PPV (%)	NPV (%)
Liao et al (2014)[45]	P	First febrile UTI	278 (75 RS)	⩽2 y	PCT to detect RS and VUR	US, DMSA, VCUG	—	—	—	—	—	—
Bressan et al (2009)[44]	P	First febrile UTI	72 (14 RS)	7 d-3 y	PCT to detect RS	DMSA VCUG	—	0.5	85.7	51	—	—
Prat et al (2003)[43]	—	First febrile UTI	77 (13 RS)	1 mo-12 y	PCT to distinguish uncomplicated vs severe UTI with RS	DMSA	0.83	1	92	92	32	98
Smolkin et al (2002)[42]	P	First febrile UTI	64 (18 RS)	15 d-3 y	PCT to distinguish uncomplicated vs severe UTI	DMSA	—	0.5	94	90	86	98
Gervaix et al (2001)[41]	P	Febrile UTI	54 (34 RS)	7 d-16 y	PCT to distinguish uncomplicated vs severe UTI	DMSA	—	0.5	74	85	—	—

Abbreviations: AUC, area under the curve; DMSA, ^{99m}Tc-dimercaptosuccinic acid; NPV, negative predictive value; PCT, procalcitonin; P, prospective; PPV, positive predictive value; R, retrospective; RS, renal scars; Sn, sensitivity; Sp, specificity; US, ultrasound; UTI, urinary tract infection; VCUG, voiding cystourethrography; VUR, vesicoureteral reflux.
[a]Cutoff value for procalcitonin. Values expressed in ng/mL.

Table 3. PCT in respiratory tract infections.

STUDY	TYPE	POPULATION	N	AGE	AIM	GOLD STANDARD	AUC	CUTOFF[a]	SN (%)	SP (%)	PPV (%)	NPV (%)	CONCLUSIONS
Korppi (2003)[51]	P	CAP confirmed by CRX. Primary health care settings	190	0-15 y	1, 2	CRX, microbial tests	0.58	0.5	46	52	—	—	PCT has no role in diagnosis of bacterial CAP in primary health care settings
Prat (2003)[47]	—	CAP. Clinical or RX diagnosis in ED	85	6 mo-10 y	1	CRX, microbial tests	0.76	2	69	80	—	—	PCT shows good S for distinguishing pneumococcal form other pneumonias. PCT can help to rationalize antibiotic therapy
Hatzistilianou (2002)[50]	P	Hospital admission for clinical pneumonia	73	2-14 y	1, 3	CRX, microbial tests	—	2	100	98	93	—	PCT is a good marker of bacterial pneumonia
Korppi (2001)[48]	P	Hospital admission for pneumonia	132	—	1, 2	CRX, microbial tests	—	1	32	88	—	—	PCT does not discriminate between viral and bacterial pneumonia
Moulin (2001)[49]	—	ED. Hospital admission for severe CAP	72	2 mo-13 y	1	CRX, microbial tests	0.93	1	86	87.5	90.2	80	PCT differentiates between bacterial and viral pneumonia
Toikka (2000)[46]	—	Hospital admission	126	1 mo-17 y	1	CRX, microbial tests	—	2	50	80	—	—	If PCT > 2 ng/mL, bacterial pneumonia is highly probable

Abbreviations: AUC, area under the curve; CAP, community acquired pneumonia; CRX, chest x-ray; ED, emergency department; NPV, negative predictive value; P, prospective study; PCT, procalcitonin; Sn, sensitivity; Sp, specificity.
1. PCT to distinguish between bacterial and viral pneumonia.
2. PCT to differentiate the specific cause of pneumonia (chlamydia, mycoplasma.).
3. PCT to reduce the antibiotic treatment.
[a]Cutoff value for procalcitonin. Values expressed in ng/mL.

- Infections in hemato-oncology

In hemato-oncology patients, PCT can be used as a marker of infection and severity,[69] although some authors emphasize that further studies are needed to define the cutoff for this protein in situations of immunologic deficit[70] (Table 4). In patients with neutropenia, PCT induction may be reduced but not inhibited, so lower limit values, probably between 0.1 and 1.5 ng/mL, would be recommendable.[70] Paraneoplastic syndromes and small cell lung cancer may induce PCT elevation.[62,71–73] Regarding localized bone infections, septic arthritis, and soft tissue infections, PCT has not been shown to be a good biomarker. It is possible that the cutoff level to differentiate this localized pathology is much lower than the one currently available.[61] There is a new ultrasensitive PCT method, which quantifies PCT levels below 0.5 ng/mL. Perhaps this ultrasensitive method[74] will play a leading role in the management of localized infectious disease in the coming years.

- Nosocomial infections

Procalcitonin in the critically ill patient is very important because of its contribution to warning of risk of nosocomial infection and its implications in life prognosis. High PCT should serve to warn about nosocomial infection in those patients without other causes of higher PCT such as cardiopulmonary arrest and some kinds of surgeries, especially with PCT levels up to 2 ng/mL.[66] It is also useful for diagnosis of catheter-related-infection in those patients in whom other infections are also under study[75] (Table 4).

Procalcitonin in extracorporeal membrane oxygenation support

The contact of the blood with extracorporeal circulation initiates activation of proinflammatory cytokines that leads to SIRS.[76] In spite of improvement in the materials of the extracorporeal membrane oxygenation (ECMO) circuit, the SIRS that is developed continues to be a problem in these patients, both adult and pediatric. There is a paucity of data about PCT kinetics after entering in ECMO support, as well as about its response to an ECMO infection. An article published in 2013 on pediatrics[63] seemed to indicate that PCT values were especially low in patients infected during ECMO. According to the authors' results, it appeared that PCT was related to patient morbidity (secondary to organ dysfunction), but not to the presence of infection. In adults, recent data shows PCT's ability to detect general postoperative complications after long-term ventricular assist device more than infectious complications.[77] However, an article on adults[64] concluded that PCT was not modified by entry into ECMO and that it might be a good biomarker of severe infection in these patients. In a recent article that analyzed 40 pediatric patients in ECMO,[78] PCT seemed to produce the expected kinetics for the pathology that conditioned ECMO support, but data about the relation of PCT and infection in ECMO are still weak (Table 4). Therefore, more studies are required to evaluate the usefulness of PCT as a biomarker of infection and morbidity in these patients.

Procalcitonin in surgical procedures

After surgery, there is frequently a SIRS with fever. It is extremely important to find a specific biomarker that could differentiate between bacterial infection and its absence, to avoid unnecessary antibiotics. In adults, studies on postoperative PCT suggest that it may increase depending on the severity, type, and duration of the procedure.[67] In children, the response of PCT also varies depending on the characteristics of the surgery. In major abdominal surgery, PCT levels may rise 2 ng/mL, especially in dirty surgery. This increase is short-lived, and PCT levels fall 24 to 36 hours after surgery. In this context, a daily determination of PCT could be helpful in detecting increases after this time, thereby alerting of infectious complications.[38] In cardiopulmonary bypass (CPB) patients, PCT may also increase in relation to CPB time, as CPB is a potent inducer of SIRS. Many factors influence this increase (anesthesia, endotoxins, trauma, and tissue ischemia).[40] In these postoperative periods, the normal cutoff values should probably start from higher normal values, around 2 ng/mL[79] and therefore it is important to monitor them daily. Values greater than 10 ng/mL should be considered as septic complications.[39,80] Although there are few studies on PCT in neonates after CPB, it appears that PCT values above 4 ng/mL at 24 hours and 5 ng/mL at 48 hours post-CBP should alert the clinician to infectious complications.[81] Procalcitonin has also been proven to be a useful tool to identify patients at risk of delayed complications after CPB in adults.[7]

However, PCT has not proved useful during the first 7 days after liver transplant in pediatric patients, taking a week to fall to normal levels (0.5 ng/mL).[82] Nevertheless, there are several studies which have proven the useful strategy of monitoring PCT values after abdominal surgery to predict infection or major complications when PCT increase is detected, especially at 48 hours after surgery.[83–85]

In newborn populations, even surgical procedures without CPB may increase serum cytokines and other inflammatory markers, interfering with postoperative infection diagnosis. Pavcnik-Arnol et al[86] and Bölke et al[87] found in their studies higher PCT levels prior to and after surgery in newborns affected by gastroschisis compared with other patients (congenital diaphragmatic hernia or intestinal atresia), explaining this difference by bacterial contamination of the exterior gastrointestinal tract and decreased intestinal circulation.

Procalcitonin usefulness in polytrauma

The evolution and utility of PCT in trauma has not been assessed to date in children. The value of PCT in traumatic adults depends on the type and severity of the trauma. In

Table 4. PCT in other situations.

STUDY	TYPE	POPULATION	N	AGE	AIM	CONCLUSIONS
Stocker (2010)[54]	P, I	NICU, GA > 34, suspected of early onset sepsis	121	<3 d	PCT-guided decision-making on antibiotic	Serial PCT measurements allowed shortening the duration of empiric antibiotic therapy 22.4 h. The age-adjusted PCT nomogram with a safety cutoff value of 10 ng/mL seems to be reasonable.
Kordek (2003)[57]	P	NICU, all newborns (preterm and term)	187	Umbilical cord	PCT for diagnosis of intrauterine IBI	AUC, 0.75 PCT cutoff 1.2 ng/mL, Sn 69%, Sp 81%, PPV 42%, NPV 93%. PCT in preterm infants with IBI is significantly higher than in term neonates.
Chiesa (1998)[58]	P	NICU, all newborns (preterm and term)	318 *143 sepsis* *175 controls*	0-48 h 3-30 d	PCT for diagnosis early and late-onset sepsis	PCT can be a marker of early onset sepsis. PCT for early detection of late-onset infections and for monitoring the follow-up of clinical course.
Hemming (2017)[69]	P	Febrile neutropenia in children with cancer	48 episodes	0-18 y	PCT for diagnosis severe IBI	PCT > 2 ng/mL is associated with increased risk of severe infection. Data suggest that the clinical decision rules are largely ineffective in risk stratification.
Fleischhack (2000)[70]	R	Febrile neutropenia in children with cancer	122 episodes	0.7-31.8 y	PCT to detected IBI. PCT to monitor response to antibiotic	PCT cutoff 0.5 ng/mL, Sn 60%, Sp 85%. PCT was superior to other parameters in the early detection of gram-negative bacteraemia and fever of unknown origin.
Ozsurekci (2016)[75]	P	Fever with unknown focus and a central venous catheter	62	1 mo-18 y	PCT for diagnosis of catheter-related bloodstream infections	AUC 0.68, PCT cutoff 1.18 ng/mL, Sn 71%, Sp 80%, PPV 77%, NPV 74%. PCT may be a useful rapid diagnostic biomarker for suspected catheter-related bloodstream infections.
Butbul-Aviel (2005)[61]	—	ED Child with fever and limp	44	15 d-19 y	PCT for diagnosis of osteomyelitis and septic arthritis	Clinical diagnosis, pus and culture. PCT cutoff 0.5 ng/mL, Sn 43.5%, Sp 100%, PPV 100%. PCT as a useful marker in the diagnosis of osteomyelitis but not in septic arthritis.
Bobillo (2018)[78]	P	PICU, assisted with ECMO	40	<18 y	Kinetics of PCT and its relationship with morbidity and mortality	PCT could be useful in the same situations as in patients without ECMO.
Sariego-Jamardo (2017)[38]	P	PICU After different types of surgery	115	—	Kinetics of PCT increase above the suggested cutoff level for PCT for the diagnosis of sepsis	PCT showed an early peak at 24 h after surgery with a rapid decrease. PCT showed no increase after clean and clean-contaminated surgery. PCT seems to be a useful tool to guide diagnosis and antibiotic approach to nosocomial sepsis in the postoperative period
Launes (2016)[95]	P	PICU Bacterial nosocomial infection confirmed by cultures	96	1 mo-18 y	To analyze results after implementation of antibiotics de-escalation protocol guided by PCT	Protocol of stewardship: PCT decreasing >50% in comparison with its value at diagnosis, or <0.5 ng/mL. After the implementation of the protocol, 75% of the children were treated for 10 days, compared with 14 days of the pre-implementation period. PCT-guided protocol reduced the exposure to antibiotics in nosocomial infections without adverse outcomes.
Rungatscher (2013)[63]	P	PICU, assisted with veno-arterial ECMO	20	<2 y	PCT for predicting infection, organ dysfunction, and clinical outcome	Higher PCT values in patients non-infected (Infected, 2.4 ng/mL and non- infected, 8.8 ng/mL). Higher PCT values in patients with multi-organ dysfunction (10.9 vs 1.85 ng/mL).
Davidson (2013)[40]	P	CICU After CS	69	<3 mo	Kinetics of PCT	PCT rises after cardiothoracic surgery but decreases by 72 h. Higher PCT levels at 72 h are independently associated with increased circulatory support at 72 h and a trend toward increased length of intubation. PCT may be better than CRP as a sepsis biomarker.

Abbreviations: AUC, area under the curve; CICU, cardiac intensive care unit; CRP, C-reactive protein; CS, cardiothoracic surgery; ECMO, extracorporeal membrane oxygenation; ED, emergency department; GA, gestational age; I, interventional study; IBI, invasive bacterial infection; NICU, neonatal intensive care unit; NPV, negative predictive value; P, prospective study; PCT, procalcitonin; PICU, pediatric intensive care unit; R, retrospective study; Sn, sensitivity; Sp, specificity.

isolated peripheral lesions, PCT induction (as opposed to CRP) is mild. In abdominal trauma, the levels increase to ranges similar to those for extensive abdominal surgery. A daily measurement is necessary for differential diagnosis (PCT progression). It is associated with increased overall risk of complications (prolonged ICU stay, severe sepsis, septic shock, and higher mortality rate).[88] It appears that PCT rises proportionally to the severity of tissue damage and hypovolemia.[89]

Procalcitonin as Antibiotic Guideline

In recent years, numerous studies, especially in adults, have been published on the usefulness of PCT as a biomarker of response to antimicrobial treatment and stewardship guided by PCT. In adults, the first report was the PRORATA trial, by Bouadma,[90] which analyzed the use of PCT to reduce patients' exposure to antibiotics in intensive care units. This multicenter randomized controlled trial evaluated adult patients with severe bacterial infection. Antibiotics were started and concluded depending on the PCT levels. The PCT-guided group had a significantly shorter antibiotic duration with respect to the control group, with an absolute difference of 2.7 days, and without any complications. Other studies in adults have demonstrated similar results,[65,91,92] as summarized in some meta-analyses of randomized controlled trials.[93,94] In pediatric PICU patients, there are few data. Launes et al[95] demonstrated a 2-day antibiotic reduction in nosocomial infections, without an increase in complications. Also in newborns with early onset sepsis, there was demonstrated to be a reduction of almost a day (22.4 hours) in antibiotic therapy[54] (Table 4).

Financial Assessment of Procalcitonin-Guided Protocols

The only data available at this time come from studies conducted in the adult population. We refer to them for their possible extrapolation to future studies in the pediatric population. Daren reviewed and analyzed previously published interventional studies, which reported reduction of antibiotic exposure in PCT-guided protocols, to determine the financial cost. There was assumed to be a mean of 2 days of antibiotic reduction overall.[96] In the PCT-guided group, the total antibiotic duration resulted in a mean of 6 days, and 8 in the non-PCT guided group. There was detected to be a 15% lower cost in the PCT group, when including antibiotic and PCT analysis. Wilke et al[97] conducted a similar study, which analyzed 6 relevant studies about PCT-guided treatment (in septic and mechanical ventilation-associated pneumonia patients) with very similar results.

Procalcitonin Limitations

Procalcitonin, like any other biomarker, needs to be used in line with patient clinical symptoms and signs and, more importantly, with medical judgment. Procalcitonin could yield false positive values in some cases. This can be seen in the first 48 hours of life in neonatal patients (physiological increase),[98,99] for example. In adults, there is more published evidence, with literature supporting an increase in the value of PCT during the first 24 to 48 hours following a major surgical procedure,[100] severe trauma,[101] or burns,[102] and in severe or prolonged cardiac shock.[24,103] The OKT3 antibody treatment and other inflammatory procytokines may raise PCT levels as well. Higher PCT baseline levels in some types of lung cancer and in thyroidal C-cell carcinoma have been reported.[104] In any case, the highest levels in these situations are not normally that high, so that PCT levels up to 10 ng/mL may be considered as a septic situation. In the same line, when PCT in these doubtful patients increases continuously, one should be on the alert for an infectious complication. At the beginning of bacterial infection cases (first 12 hours of evolution), in localized infections, and in subacute endocarditis, PCT levels may be inappropriately low, so caution in monitoring may be indicated in these patients. Most of these limitations may be avoided with close PCT monitoring, especially at the beginning of a clinical situation that suggests analyzing this biomarker.

Conclusions

Procalcitonin seems to be a good biomarker to diagnose and monitor critically ill pediatric patients with mild-to-moderate as well as severe bacterial infections. Procalcitonin also seems to decrease antibiotic exposure and it shortens the PICU stay. However, more studies are needed to confirm its usefulness for stewardship as has already been demonstrated in adults.

Author Contributions

JRF, IJS and BP designed the review. RF and BP wrote the first draft of the manuscript. IJC revised all the different drafts and reviews of the manuscript. All authors reviewed and approved final version of the manuscript.

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