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Original research article

Monitoring both procalcitonin and C-reactive protein in the early period after tetralogy of Fallot correction in children promotes rational antibiotic use

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ABSTRACT

Purpose: This retrospective cohort study aimed to identify the early postoperative kinetics of C-reactive protein (CRP) and procalcitonin (PCT) in children undergoing tetralogy of Fallot (ToF) correction. The ability of these inflammatory markers to guide rational antibiotic usage was also determined.
Materials and Methods: All consecutive children who underwent ToF correction in 2009–2016 in our referral pediatric cardiac surgery clinic in Gdansk, Poland and did not exhibit infection signs on early postoperative days (POD) were identified. All patients received 48 h antibiotic prophylaxis. Antibiotic treatment was extended or empirical antibiotic therapy was introduced if the clinician considered it necessary. CRP and PCT levels were measured on POD1–4 and 1–3, respectively.
Results: Of the 60 eligible children, 44 underwent CRP testing only. The remaining 16 patients underwent both CRP and PCT testing. All patients had abnormally high CRP values after surgery. All patients who also underwent PCT testing also displayed elevated PCT levels. The CRP and PCT levels peaked on POD2 (median = 99.8 mg/L) and POD1 (median = 4.08 ng/mL), respectively. In the CRP-alone patients, antibiotic prophylaxis was prolonged or empirical antibiotic therapy was started in 59%; in the CRP and PCT group, this was 25% ($p < 0.05$).
Conclusions: The children had elevated CRP and PCT levels after ToF correction, with peaks observed on POD2 and POD1, respectively. Monitoring both CRP and PCT in the early postoperative period may guide antibiotic therapy, thus reducing unnecessary treatment, additional toxicity, and adverse drug interactions without increasing treatment failure. Rational antibiotic treatment may also reduce antibiotic resistance.

1. Introduction

Starting in the early 1990s, PCT levels have been used in clinical settings as a marker of bacterial infection. It was also shown that this marker is more specific and sensitive for this purpose than other commonly used acute phase markers such as C-reactive protein (CRP) [1]. However, it was later found that PCT and CRP levels not only rise in response to microbial acute phase stimulants; they also increase after surgery, burns, blood transfusions, and many other clinical situations. Also, cardiac procedures involving extracorporeal circulation (ECC) induce a nonspecific acute immune reaction termed systemic inflammatory response syndrome (SIRS), which is associated with elevated PCT and CRP levels.

In 2006, the Society of Thoracic Surgeons (STS) released their guidelines regarding the use of prophylactic antibiotics after cardiac surgery: it was recommended to limit prophylactic antibiotics to 48 h postoperatively. However, while this practice has now been widely adopted in adult cardiac surgery, it is often not followed in pediatric cardiac surgery [2]. Indeed, it is not uncommon that, after 48 h of routine antibiotic prophylaxis, the treatment is prolonged or new antibiotic therapy is prescribed. The reasons given for this include the “personal experience” of the attending physicians in empirical antibiotic therapy and/or the

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deterioration of or uncertainty regarding the condition of the patient. However, this caution may not be warranted: in 2016, Bath et al. showed that restricting antibiotic prophylaxis to 48 h after pediatric cardiac surgery does not increase the incidence of surgical-site infections [3]. Moreover, it is becoming increasingly important to reduce antibiotic consumption to the absolute minimum because of increasing rates of antibiotic-resistant bacteria and superinfections in pediatric intensive care units.

Acute phase markers may be useful when deciding when it is safe to adhere to the 48-h limitation of perioperative antibiotic therapy after pediatric cardiac procedures. However, to exploit this possibility, it is important to know how acute phase marker kinetics change in the early postoperative period after pediatric cardiac procedures.

The aim of this retrospective cohort study was to determine how the PCT and CRP levels in children change early after surgical correction of tetralogy of Fallot (ToF) with ECC. Moreover, it aimed to determine whether measuring PCT as well as CRP associates with more rational antibiotic treatment in children lacking clinical signs of infection early after surgery.

2. Material and methods

This retrospective cohort study was approved by the local ethics committee (no. 178/2012) and adhered to the tenets of the Declaration of Helsinki and its revisions. The need for informed consent was waived due to the retrospective nature of the study.

2.1. Patient selection

All consecutive children with ToF who were referred in 2009–2016 to our pediatric cardiac surgery clinic for primary ToF surgical correction with ECC were assessed for study eligibility. The inclusion criteria were lack of clinical signs of infection and absence of organ dysfunction, as determined by laboratory values, preoperatively. Patients were excluded if they met one or more of the following criteria: they had a congenital heart disease that was not ToF; their body weight was less than 2.5 kg; they had uncompensated hypothyroidism; they had clinical signs of an acute infection (including fever, diarrhea, cough, and urinary tract infection); their preoperative serum CRP and/or PCT values exceeded 5 mg/L and 0.5 ng/mL, respectively; they exhibited leukocytosis; they underwent perioperative steroid treatment; the index surgery was reoperation after previous ToF correction; and/or they died less than 3 days after surgery due to reasons other than infection.

2.2. Preoperative and operative procedures

All patients underwent routine preoperative echocardiography, chest X-ray examination, electrocardiography, and complete blood count and biochemistry analysis. All patients were also routinely screened for infection at admission, as required by our individually designed institutional practice [4].

General anesthesia was induced and maintained according to routine standards. Surgery was performed *via* median sternotomy with standard aorta and direct bicaval venous cannulations. Heparin was then administered (300 IU/kg body weight). A nonpulsatile roller pump (Sorin S5^{TM}) equipped with custom-made oxygenation and veno-arterial drains was used. If present, systemic-to-pulmonary shunts (modified Blalock-Taussig) were closed just after initiating bypass. Mild hypothermia (28–32 °C) during ECC and cardiac arrest with standard antegrade cold crystalloid cardioplegia were used. Hematocrit values were maintained above 30% during the ECC rewarming period with continuous hemofilatration commenced in the circuit. The right ventricular outflow tract obstruction (RVOTO) was widened though the right atrium and tricuspid valve using muscular excessive trabeculation resection. Cases of conal, valvular, and supravalvular obstruction underwent direct RVOTO reconstruction augmented with Contegra® xenograft implantation following a 'mono-cusp' technique. Malaligned ventricular septal defects were closed using a Gore-Tex® cardiovascular patch and a running monofilament suture technique. If necessary, tricuspid valve repair was performed in the area of the ventricular septal defect patch. Weaning from ECC and closing of the chest were performed by routine methods.

2.3. Postoperative care

All patients were thoroughly monitored postoperatively for signs of infection by clinical examinations, chest radiography, and laboratory and microbiological tests. Patients who were suspected of having an infection underwent routine microbiological examinations such as bronchial secretion, blood, and urine samples for culture. All children received perioperative antibiotic prophylaxis according to our institutionally designed in-hospital standards. In the first 2 years of the study period (2009–2010), the antibiotic prophylaxis consisted of amoxicillin and clavulanic acid. Thereafter (2011–2016), cefazolin became the antibiotic of choice in our department. It was given intravenously at 30 mg/kg 15–60 min before intervention. This administration was repeated every 3–4 h during surgery. Cefazolin was also administered at 30 mg per 100 mL of heart-lung machine priming while ECC was being initiated. After surgery,30 mg/kg cefazolin was given every 6 h until postoperative day (POD) 2. In the case of allergy against beta-lactams, clindamycin and gentamycin were electively used. Normally, the perioperative antibiotic prophylaxis was stopped after 48 h after surgery. However, in some cases, antibiotic prophylaxis was prolonged or an empirical antimicrobial treatment was introduced at 48 h. The final decision to prolong or introduce new antibiotic prophylaxis was left to the clinician in charge because there are no precise guidelines for reliably diagnosing infections in children early after cardiac surgery. The clinicians based their decision on the child's clinical status, indirect signs of possible infection, inflammatory markers and personal clinical experience. The clinicians were informed that decrease in CRP and/or PCT values in consecutive postoperative days might deny infection. Children who had a critical clinical status and low cardiac output 48 h after surgery were also started on empirical antifungal prophylaxis therapy (fluconazole) [5]. Steroids were not given routinely.

Blood samples were collected on POD 1, 2, 3, and 4 as part of our routine laboratory testing after surgery. All were sent to the local laboratory. Serum CRP concentrations were measured on POD 1–4 using a turbidimetric immunoassay. Serum PCT concentrations were measured on POD 1–3 using an electrochemiluminescence immunoassay. Serum CRP and PCT concentrations were considered to be correct if they were below 5 mg/L and 0.5 ng/mL, respectively. It should be noted that only some of the patients underwent both CRP and PCT testing: the majority underwent CRP testing only.

2.4. Data analyses

We assessed the kinetics of CRP and PCT levels after surgery and the type of antibiotics used in empirical therapy. To determine whether measuring both CRP and PCT promoted rational antibiotic usage relative to only measuring CRP, the CRP+PCT group was compared with the CRP-alone group in terms of the frequency with which the patients underwent prolonged antibiotic prophylaxis or received empirical antibiotic therapy after 48 h. The overall

microbiologically proven infection rates of both groups were also determined.

2.5. Statistical methods

Continuous demographic and perioperative variables were expressed as median, standard deviation (SD), and range. Categorical demographic and perioperative variables were expressed as absolute frequencies and percentages. Patient groups were compared in terms of continuous variables by first assessing the normality of the data distribution using the Kolmogorov-Smirnov test. The groups were then compared in terms of normally distributed variables using Student's *t*-test (to examine the equality of the means) and Levene's test (to examine the equality of variances). For non-normally distributed variables, the groups were compared using the Mann-Whitney *U* test. Patient groups were compared in terms of categorical variables using the Pearson chi-squared test with Fisher's exact test if necessary. The CRP and PCT levels on different postoperative days were compared using the repeated measures ANOVA with Greenhouse-Geisser correction if Mauchly's test indicated that the assumption of sphericity had been violated and post hoc tests using the Bonferroni correction had been performed. Linear correlations between preoperative saturation levels, ECC time, and AoX time with postoperative CRP and PCT levels were assessed using Pearson correlation. Differences were considered significant when *p*-values were below 0.05. All statistical analyses were performed using SPSS v. 20.0 (SPSS Inc., USA).

3. Results

3.1. Patient characteristics

In total, 63 patients underwent ToF correction during the study period. Three were excluded because they died in the first 72 postoperative hours ($n = 2$) or the index surgery was a repeat operation because of increased intraventricular pressure gradient due to right ventricle and septal hypertrophy ($n = 1$) (Fig. 1).

The median age of the remaining 60 eligible children was 6.1 (SD = 4.7, range = 2.2–35.5) months. The median weight was 6.7 (SD = 1.3, range = 2.9–11.1) kg, and 34 patients were boys (56.7%) and 26 were girls (43.3%). Sixteen patients underwent both CRP and PCT monitoring in the early postoperative period. The remaining 44 patients underwent CRP monitoring only. These two groups did not differ in terms of demographic variables or the frequency with which preoperative percutaneous interventions (RVOTO balloonplasty) and Blalock-Taussig shunts (both: right and left) were performed. They also did not differ in terms of preoperative peripheral saturation levels, ECC time, aortic cross-clamp (AoX) time, or type of ToF correction (Table 1).

3.2. CRP and PCT kinetics in the early postoperative period

All 60 children exhibited elevated CRP levels above the normal range (>5 mg/L) in the early postoperative days after ToF correction. A repeated measures ANOVA showed that mean CRP concentration differed significantly between POD 1, 2, 3 and 4 ($F(1.41, 83.4) = 59.9$, $p < 0.001$). Post hoc tests using the Bonferroni correction revealed a significant increase in CRP concentration between POD 1 and POD 2, and significant decreases between POD 2 and POD 3, and POD 3 and POD 4 (mean CRP in POD 1, 2, 3 and 4 were 50.6 ± 3 mg/L, 111.4 ± 9.1 mg/L, 78.9 ± 7.8 mg/L and 37.8 ± 3.4 mg/L, respectively; $p < 0.001$). In almost all patients ($n = 56$, 93.3%), the POD 2 CRP values were higher than the POD 1 values. Moreover, in most patients ($n = 55$, 91.7%), the POD 2 CRP levels were higher than the POD 3 levels. Thus, the CRP values generally peaked on POD 2 (Table 2 and Fig. 2).

All 16 PCT-tested patients had abnormally high PCT levels (>0.5 ng/mL) early after surgery. A repeated measures ANOVA showed that mean PCT concentration differed significantly between POD 1, 2, and 3 ($F(1.04, 15.6) = 6.65$, $p = 0.02$). Post hoc tests using the Bonferroni correction revealed a decrease in PCT concentration between POD 1 and POD 4 (mean PCT in POD 1, 2, and 3 were 10.3 ± 14.5 ng/mL, 7.5 ± 11.2 ng/mL, and 4.7 ± 8.2 ng/mL, respectively); however, pair wise comparison was not statistically significant ($p > 0.05$). In all (93.8%) except of one patient, the PCT values on POD 1 were higher than on POD 2. Thus, the PCT values generally peaked on POD 1 (Table 2 and Fig. 3).

3.3. Association of CRP and PCT levels with perioperative characteristics

The patients who had a B-T shunt or a balloon plasty preoperatively or underwent Contegra® implantation tended to

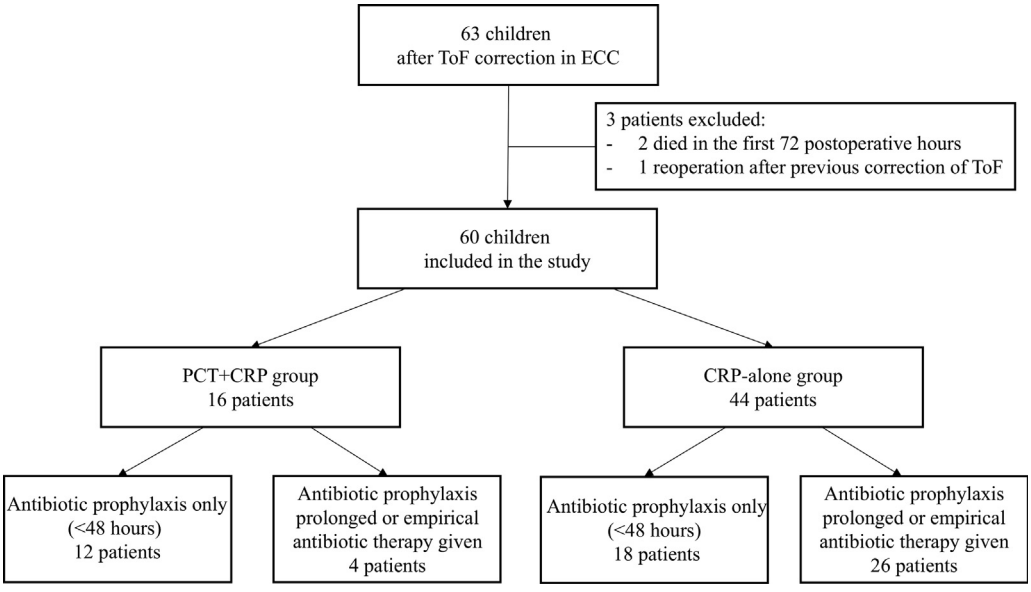

Fig. 1. Flow diagram of the patients included in the study (ECC, extracorporeal circulation; PCT, procalcitonin; CRP, C-reactive protein).

Table 1
Demographic and perioperative characteristics of 60 patients who were referred for tetralogy of Fallot correction and underwent postoperative C-reactive protein monitoring with or without procalcitonin monitoring.

	CRP + PCT group (median; SD; range)	CRP-alone group (mean; SD; range)	p-value*
Age, months	6.9; 3.1; 3–15.8	5.7; 5.2; 2.2–35.5	0.304
Weight, kg	6.4; 1.4; 5–10.9	6.9; 1.3; 2.9–11.1	0.403
Gender, male:female	8:8	26:18	0.53
Balloon plasty, no:yes†	8:8	21:23	0.876
B-T shunt, no:yes‡	11:5	25:19	0.404
Preoperative saturation, %	93; 6.4; 75–98	90; 7; 72–100	0.847
ECC time, min	120; 35; 66–190	128; 28; 80–195	0.345
AoX time, min	62; 21; 26–88	57; 18; 30–105	0.139
Transanular patch (Contegra®), no:yes	6:10	15:29	0.807

CRP – C-reactive protein; PCT – procalcitonin; SD – standard deviation; B-T – Blalock-Taussig; ECC – extracorporeal circulation; AoX – aortic cross-clamp.
* P-values were determined by comparing the two groups with Student's *t*-test and Levene's test or Mann-Whitney *U* test.
† Minimum one balloon plasty.
‡ Minimum B-T shunt.

Table 2
C-reactive protein and procalcitonin levels in children during the first postoperative days after surgical correction of tetralogy of Fallot.

Postoperative day	CRP, mg/L (median; SD; range)	PCT, ng/mL (median; SD; range)
POD1	47.6; 23.2;12.1–99.7	4.08; 14.5; 0.12–45.71
POD2	99.8; 70.7; 22.5–365.7	2.42; 11.23; 0.08–41.42
POD3	68.5; 60.3; 4–327.7	1.72; 8.23; 0.27–33.5
POD4	34.9; 25.9; 4.3125	–

CRP – C-reactive protein; PCT – procalcitonin; POD – postoperative day; SD – standard deviation.

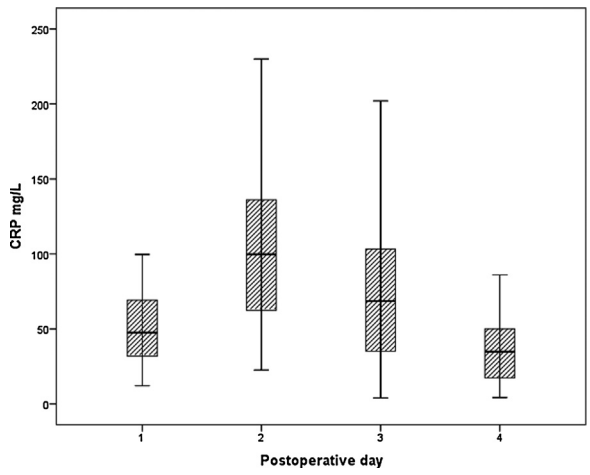

Fig. 2. C-reactive protein (CRP) values of children during the first 4 postoperative days after tetralogy of Fallot correction.

have higher CRP and PCT levels than the patients who did not undergo bioprosthesis implantation. However, these differences did not achieve statistical significance (Table 3). The preoperative saturation levels, ECC time, and AoX time did not correlate with postoperative CRP and PCT values.

3.4. Effect of CRP and PCT testing on antibiotic prophylaxis prolongation or new antibiotic therapy and postoperative infection

Antibiotic prophylaxis was prolonged or an empirical antibiotic therapy was started in 26 (59%) of the 44 CRP-alone patients. By contrast, the result was 25% ($n = 4$) for the 16 CRP + PCT patients ($p < 0.05$).

There were no differences both in CRP as well as in PCT values between patients who received antibiotic prophylaxis only and patients with antibiotic therapy exceeding 48 h postoperatively. Mean CRP in POD 1, 2, 3 and 4 in these two groups of patients were 45.5 ± 3.8 mg/L and 55.8 ± 4.5 mg/L ($p = 0.098$), 92 ± 8 mg/L and 130.8 ± 15.8 mg/L ($p = 0.128$), 62.4 ± 6.9 mg/L and 95.4 ± 13.4 mg/L ($p = 0.115$), 33.2 ± 3.9 mg/L and 43 ± 5.4 mg/L ($p = 0.225$), respectively (Fig. 4). Mean PCT in POD 1, 2, and 3 in these two groups of patients were 5.8 ± 1.8 ng/mL and 14.8 ± 10.4 ng/mL ($p = 0.48$), 7.5 ± 3.6 ng/mL and 8.9 ± 5.7 ng/mL ($p = 0.602$), 5.3 ± 2.9 ng/mL and 4 ± 2.2 ng/mL ($p = 0.602$), respectively.

The antibiotics used for empirical therapy after standard perioperative prophylaxis were amoxicillin and clavulanic acid (with or without netylmycinin eight and five children, respectively), cephalosporin III generation (with or without vancomycin in one and five children, respectively), piperacillin with tazobactam (four patients), and meropenem (with or without vancomycin in six and one patient, respectively).

None of the CRP-alone and CRP + PCT patients developed microbiologically proven infections within the first 5 days. Thereafter, however, one child who was treated with meropenem and vancomycin starting on POD 3 exhibited further clinical status deterioration (general condition) on POD 6. Microbiological examination revealed bacteremia in three independently obtained blood samples (*Eschericha coli*with extended-spectrum beta-lactamases). Another patient developed microbiologically proven candidemia (*Candida parapsilosis*) on POD 10 despite receiving empirical meropenem, vancomycin, and fluconazole starting on POD 3. None of the children developed surgical-site infections. One patient died on POD 21 because of a cerebral hemorrhage that occurred on POD 15. All other patients survived up to discharge from hospital. Thus, the hospital mortality rate in the 60 patients was 1.67%. The median postoperative hospital stay was 8 (SD = 10, range = 4–74) days. The median duration of follow-up was 43 (SD = 26.6, range = 1–91) months.

4. Discussion

This study showed that monitoring PCT as well as CRP in the early postoperative period after pediatric cardiac surgery in ECC reduced the rate of antibiotic prophylaxis prolongation or introduction of empirical antibiotic therapy after 48 h. It also

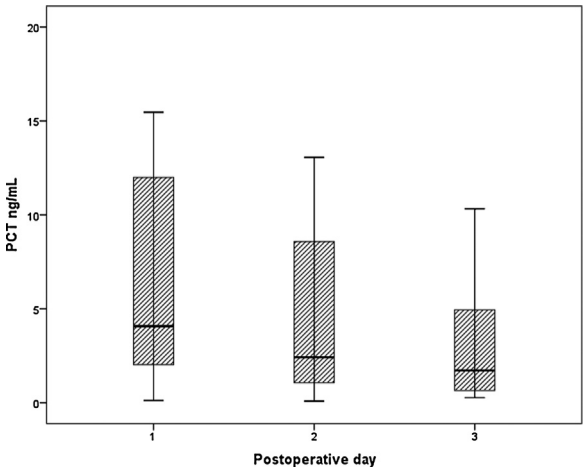

Fig. 3. Procalcitonin (PCT) values of children during the first 3 postoperative days after tetralogy of Fallot correction.

showed that, in the vast majority of patients, the CRP and PCT levels peaked on POD 2 and POD 1, respectively. We think, that decrease in CRP and/or PCT values in early postoperative period after pediatric cardiac surgery in ECC has influence on clinicians decision about antibiotic treatment. Decrease and not absolute value of these inflammatory markers might be an argument not to suspect infection beginning in this group of patients. The lower rate of antibiotic prophylaxis prolongation or an empirical antibiotic therapy introduction in CRP + PCT patients than in CRP-alone patients after surgery in ECC might be probably caused by the knowledge of clinicians of decreasing level mainly of PCT between POD 1 and POD 2. The knowledge of CRP and PCT kinetics may aid clinical decision-making, especially in cases where there are doubts about whether discontinuing antibiotic prophylaxis after 48 h is safe.

At present, there are no definitive guidelines regarding proper antibiotic prophylaxis in children undergoing cardiac surgery, especially in relation to the length of the therapy. However, as Jennifer C. Romano indicated in her recent editorial commentary, there are many reasons why limiting the duration of antibiotic prophylaxis after pediatric cardiac surgery should be considered [2]. In particular, there is evidence that it may help to curb the increasing emergence of antibiotic-resistant bacteria and super-infections in pediatric intensive care units [2]. Moreover, there is recent evidence that suggests that limiting antibiotic prophylaxis does not negatively influence surgical outcomes [2]. These suggest that centers should consider changing their antibiotic prophylaxis regimes [2]. Clearly, the present study suggests supporting this argument. Since surgical site infections and sepsis are serious complications of cardiac surgery and are associated with high mortality rates, the prognosis can be significantly improved by early therapeutic intervention [6,7]. Thus, it is essential to rapidly and accurately diagnose clinically relevant bacterial infections after open heart surgery. However, we wish to stress that, to achieve good outcomes with routine antibiotic prophylaxis limitation, it is vital that the complex approach that is standardized in our clinic is also followed. This approach includes preoperative microbiological screening, proper preoperative patient preparation with an antiseptic bath, institution of a hand-hygiene program, antibiotic prophylaxis, and aseptic surgical and urinary and central venous catheterization techniques. All of these factors can significantly influence the final outcomes of pediatric cardiac surgery [4,8].

At present, diagnostic CRP and PCT cut-off values in the early postoperative period that help clinicians detect infections in patients after surgery with ECC have not been established [9–11]. However, clinicians use described markers in a clinical setting. In a nationwide questionnaire sent to adult cardiac surgery centers in Germany with a response rate of 87%, 97% and 74% responded measuring CRP and PCT for postoperative sepsis diagnosis, respectively [12]. The clinical usefulness of PCT for infection diagnosis remains unclear because multiple studies show that PCT values are significantly affected by surgical factors. First, several studies showed that early postoperative PCT values are affected by

Table 3
Postoperative C-reactive protein and procalcitonin levels in children grouped according to type of tetralogy of Fallot correction, preoperative balloon plasty, and B-T shunts in early postoperative days.

		POD1		POD2		POD3		POD4	
		(mean; SD; range)	*p*-values*	(mean; SD; range)	*p*-values*	(mean; SD; range)	*p*-values*	(mean; SD; range)	*p*-values*
				C-reactive protein (mg/L)					
Correction with xenograft	yes (n = 39)	53; 24.2; 12.4–99.7	0.304	115; 73.5; 22.5–365.7	0.625	86; 65.1; 10–327.7	0.236	41; 28; 4.3–125	0.201
	no (n = 21)	46; 21; 12.1–83.2		105; 66.3; 22.5–365.7		65; 48.6; 4–182.3		31; 20.4; 7.3–74	
Balloon plasty†	yes (n = 31)	53; 20.6; 23–95.4	0.398	110; 57.8; 23–294.1	0.534	77; 50.5; 4–202	0.847	41; 29.7; 5–125	0.539
	no (n = 29)	48; 25.7; 12.1–99.7		113; 83.4; 22.5–365.7		81; 70.1; 13.6–327.7		34; 21; 4.3–80	
B-T shunt‡	yes (n = 24)	58; 23.7; 12.4–99.7	0.34	123; 58.5; 29–260	0.062	88; 52.6; 13.6–217	0.12	45; 29; 4.3–125	0.135
	no (n = 36)	46; 21.6; 12.1–95.4		104; 77.7;22.5–365.7		73; 64.9; 4–327		33; 22.9; 5–86	
				Procalcitonin (ng/mL)					
Correction with xenograft	yes (n = 6)	12.8; 17.4; 0.28–45.71	0.492	9.1; 13.6; 0.29–41.4	0.492	5.7; 10.2; 0.27–33.5	0.792	–	
	no (n = 10)	6.2; 7.2; 0.12–15.5		4.7; 5.7; 0.08–13.1		2.9; 3.1; 0.52–7.6		–	
Balloon plasty†	yes (n = 8)	10.8; 14.9; 0.3–45.7	0.6	6.9; 8.6; 0.3–25.7	0.529	3.2; 3.4; 0.3–10.3	0.916	–	
	no (n = 8)	9.8; 15.1; 0.1–45		8; 14; 0.1–41.4		6.2; 11.3; 0.5–33.5		–	
B-T shunt‡	yes (n = 5)	12.9; 18.6;0.1–45.7	0.777	7.6; 10.4;0.1–25.7	0.865	3.3; 4.1; 0.5–10.3	0.955	–	
	no (n = 11)	9.1; 13.1; 0.3–45		7.4; 12.1;0.3–41.4		5.3; 9.7; 0.3–33.5		–	

POD – postoperative day; SD – standard deviation.
* *p*-values were determined by comparing the two groups with Student's *t*-test and Levene's test or Mann-Whitney *U* test.
† Minimum one balloon plasty.
‡ Minimum B-T shunt.

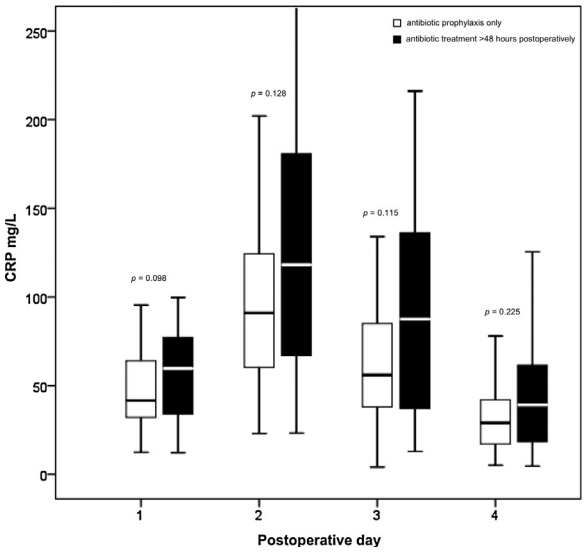

Fig. 4. C-reactive protein (CRP) values of children during the first 4 postoperative days after tetralogy of Fallot correction who received antibiotic prophylaxis only and with postoperative antibiotic therapy exceeding 48 h.

the type of surgery, ECC time, degree of hypothermia, degree of organ ischemia and insufficiency, and use of hemofiltration, vasopressor support, and blood compound supplementation [1,13]. Second, Minami et al. found that PCT levels during the early postoperative period may relate to postoperative severity or organ failure, and can serve as a predictor of these outcomes [14]. Third, a study on pediatric patients undergoing cardiac surgery with ECC showed that long ECC and AoX times associate with a marked elevation of SIRS-induced PCT levels on POD 1 [15]. Fourth, several authors have concluded that, although PCT values below 5.0 ng/mL do not associate with postoperative complications in cardiosurgical patients, higher PCT levels early after surgery do correlate significantly with the length of stay in the intensive care unit, time on mechanical ventilation, and duration of inotropic support [9,16,17]. Finally, several studies found that elevated PCT levels in adult patients after cardiopulmonary bypass are not a good indicator of bacterial infections, especially in patients with acute kidney injury [18,19]. Thus, there is no consensus regarding the role of PCT and the cut-off values in pediatric cardiac surgery that allow infection-related inflammation to be distinguished from SIRS-related inflammation. The same issue concerns the role of CRP in clinical decision-making after pediatric surgery with ECC. Some authors state that CRP can be used to diagnose infections while others argue that CRP cannot be used for this purpose because of the SIRS-induced postoperative elevation of CRP [1,20–22]. Nevertheless, there are also multiple studies that suggest that CRP and PCT are useful tools for guiding antibiotic treatment after cardiac surgery and may help to avoid delayed or unnecessary antimicrobial therapy [23]. First, Maravić-Stojković et al. suggested that PCT-guided antibiotic treatment in adult cardiac surgery can be safe and cost-effective in postoperative care [13]. Second, Pierce et al. concluded that PCT is a reliable serum marker for determining the presence or absence of an invasive bacterial infection and response to antibiotic therapy [24,25]. Third, antibiotic therapy that is tailored by serial PCT measurements may shorten antibiotic exposure without increasing treatment failure [13,26]. This possibility is supported by the CRP and PCT kinetics that we observed in the present study: they suggest that kinetic analysis and repeated measurements of serum CRP and PCT instead of their absolute value scan help detect an evolving infection in children early after ToF correction with ECC.

Our study cohort consisted only of patients who underwent ToF surgical correction which in contemporary practice involves a wide spectrum of different clinical settings, surgical techniques, and anatomical variation. Therefore, there are marked differences worldwide in terms of surgical approach and cooperation with interventional cardiology treatment. In our institution, we treat ToF cases with aggressive percutaneous intervention involving RVOTO balloon angioplasty; we also close all sources of peripheral pulmonary shunts before surgical correction and use only xenografts for RVOT reconstruction. We did not find that these significant influenced early postoperative CRP and PCT values. Notably, our perioperative strategy aiming to prevent infectious complications in our center seems to be effective because surgical-site infections did not arise in the early postoperative period.

Notably, we used a wide range of non-cefazolin antibiotic types for empirical therapies relatively frequently. Thus, local recommendations regarding first-line empirical antibiotic therapy in pediatric patients after ToF correction would be useful. However, the factors that should underpin these recommendations are currently unknown. They may include the local microbial resistance map, preoperative pathogen colonization studies, or other factors. Future studies on this issue are warranted.

4.1. Study limitations

This study had several limitations. First, it was a retrospective observational single center study with a small sample consisting of carefully selected small children who underwent cardiosurgical correction of ToF in ECC. This study design may introduce selection and information bias and be of limited generalizability. Second, the antibiotic prophylaxis algorithms that were used during the study period were not homogenous. Thus, the CRP and PCT kinetics that we observed may not be observed with other antibiotic treatment approaches. However, when we excluded patients who underwent antibiotic prophylaxis with agents other than cefazolin, the outcomes and conclusions were the same (data not shown). Third, the perioperative care practices at our institution for patients with ToF may differ from the practices used in another centers. Therefore, the presented data should be interpreted and extrapolated with caution. Further prospective studies are needed.

5. Conclusions

This study showed that all children who underwent ToF correction had abnormally high CRP and PCT values in the early postoperative days, and these values peaked on POD 2 and POD 1, respectively. Irrespective of absolute values in next POD both inflammatory markers decrease in the absence of infection. These kinetics of both inflammatory markers may help guide postsurgical antibiotic treatment, thereby reducing unnecessary treatment and preventing the development of resistance in the natural microbiota without increasing treatment failure. The fact that CRP and PCT could be used to reduce microbial resistance is particularly important given the increasing rates of antibiotic-resistant bacteria and superinfections in pediatric intensive care units [27]. Research that yields proper early postoperative care guidelines for surgically treated children with congenital heart disease is warranted.

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Conflict of interest statement

The authors declare no conflict of interests.

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