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FELLOWS FORUM

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Ductus arteriosus-associated infective endarteritis: Lessons from the past, future perspective

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Abstract

Background: Since routine clinical use of antibiotics as well as surgical and catheter-based closure of a patent arterial duct (PDA), PDA-associated infective endarteritis (PDA-IE) is rare but can still occur when the ductus is still open or as it closes. Thus, clinicians should maintain a high index of concern for patients with unexplained fever.

Methods: We report on a PDA-IE in a young infant shortly after potentially delayed obliteration of a PDA. We discuss this case report by reviewing the literature in regard to the pathogenesis (infection primary or secondary to PDA thrombus formation), clinical (new heart murmur) and diagnostic findings (transthoracic echocardiography, total body MRI, laboratory findings), and clinical outcome during mid-term follow-up after successful antibiotic treatment.

Results: A 7-week-old term infant with *Staphylococcus aureus* sepsis and a new heart murmur was diagnosed with PDA-IE by transthoracic echocardiography at the pulmonary artery end of an obliterated PDA. Broad diagnostic workup excluded other reasons for sepsis. After 4 weeks of antibiotic treatment the vegetation reduced in size and the infant recovered completely. A review of all cases of PDA-IE (in pediatric and adult patients) previously published was performed.

Conclusion: Nowadays, a PDA-IE is an extremely rare, but still life-threating condition that may even affect patients with a nonpatent ductus arteriosus shortly after its obliteration and should be considered as infective complication in preterms, neonates, and small infants. Therefore, in septic neonates with bacteremia, transthoracic echocardiography may be integrated in the diagnostic workup, especially by fever without source and clinical signs of IE such as a new heart murmur.

KEYWORDS

bacteremia, infective endarteritis, infective endocarditis, patent ductus arteriosus, sepsis

1 | INTRODUCTION

The clinical pattern and epidemiology of pediatric infective endocarditis (IE) in developed countries has substantially changed due to advances of medical care including routine antibiotic treatment for bacterial infections, improvements in pediatric cardiac surgery, and catheter interventional treatment and prophylactic recommendations regarding IE in patients at risk.[1,2] Nowadays, IE normally remains a rare disease, but associated with relevant morbidity and mortality in affected patients.[1,2] In fact, due to the decline of rheumatic fever, predisposing factors for IE in children are more often related to congenital heart disease (CHD) and its subsequent surgical

correction or palliation with use of foreign material (normally pulmonary valve infections)[1,2] Native valve infections in preterm and immune-compromised infants are also described.[1,2]

The ductus arteriosus Botalli connects the descending aortic arch with the roof of the main and left pulmonary artery and serves as an obligatory right-to-left shunt during fetal life. Since first successful surgical ligation of a patent ductus arteriosus (PDA) in 1938[3] and the establishment of medical and interventional techniques for PDA closure, infective endarteritis in patients with a PDA is a rare or even disappearing clinical entity in developed countries and only described in cases reports[4-35] and one retrospective study[36] with vegetations related to hemodynamic relevant or less relevant PDA found either in *postmortem* studies or echocardiographic evaluations. However, in developing countries a PDA remains a predisposing risk factor for IE.[27,36,37]

We present the case of a 7-week-old infant with an IE (better termed as endarteritis) of the pulmonary artery at the entrance of a former PDA.

2 | CASE PRESENTATION

A 7-week-old male term born was seen at our pediatric emergency room with a history of fever and impaired clinical status. He had been delivered with a planned cesarean section at 38 4/7 postmenstrual weeks (birth weight 3060 g) after an uneventful pregnancy and an unremarkable postpartal adaptation. Breast-feeding was performed and no failure to thrive or signs of infection were noticed. At the age of 3 days and 4 weeks, two regular pediatric checkups were performed without relevant findings except a transient redness of the umbilicus, that we could not see at admission. In the family, there was no history of cardiac diseases, immune deficiencies, or coagulation disorders.

On admission at the age of 7 weeks, he presented with high fever (up to 40°C) without a focus. Environmental history was negative for infections. The clinical examination showed a well fed, not dysmorphic infant with fever without focus and tachycardia. After volume bolus and sampling of cerebrospinal fluid (CSF), blood and urine, and empirical antibiotics (amoxicillin and gentamicin) were started under the suspicion of sepsis. Blood cultures grew *Staphylococcus aureus* with a time to positivity (TTP) of 8 hours. Antibiotic treatment was changed according to the antibiogram to monotherapy with flucloxacillin. The day after, total body magnetic resonance imaging (MRI) and abdominal ultrasound excluded osteomyelitis or an abdominal focus. A new harsh 2/6 systolic crescendo-decrescendo heart murmur with punctum maximum at the left second intercostal space 2 cm to the sternal boarder with normal heart sounds without irradiation was noticed. Transthoracic two-dimensional echocardiography showed a hyperechogenic mobile moderately flattering mass (8 × 3 mm) at the roof of the left pulmonary artery (LPA) near the former opening of a meanwhile completely closed PDA (Figure 1A). The finding was consistent with a thrombus formation respectively vegetation downstream directed from the former flow direction at the low-pressure opening of a now obliterated PDA. The blood flow in the LPA was slightly accelerated by a systolic pulse wave Doppler gradient of V_{max} 180 cm/s compared to the right pulmonary artery (V_{max} 141 cm/s). There were no further pathological findings at echocardiography. Total body MRI specifically showed no signs of embolisms in the pulmonary arteries and no pathological signs in the lungs' parenchyma. After 36 hours of antibiotic treatment blood cultures were negative, the patient was afebrile, and the clinical status improved. Due to the clinical course, blood examinations, and response to antibiotic therapy, together with the results of the imaging modalities ruling out any other focus for infection, the diagnosis of an infective *S. aureus* endarteritis at the LPA was made. After 1 week of treatment, echocardiographic follow-up (Figure 1B) determined unchanged dimension of the vegetation, but a higher echogenicity; inflammation parameters had almost normalized (CrP 4 mg/L, erythrocyte sedimentation rate (ESR) 25 mm/h). After 2 weeks (Figure 1C) and 4 weeks (Figure 1D) of treatment, echocardiography revealed smaller dimensions of the vegetation with, respectively, 5 × 4 mm and 5 × 3 mm with normal Doppler blood-flow pattern in LPA. Laboratory analysis showed a complete normalization of inflammation parameters and a normal coagulation profile. The child was discharged in good clinical status without a heart murmur. Nine weeks after fever onset and 5 weeks after the end of antibiotic treatment, the child was asymptomatic. Echocardiographic findings were unchanged with residual vegetation (Figure 1E). An immunological evaluation was performed without pathological finding.

3 | DISCUSSION

At the beginning of the last century, PDA-associated infective endarteritis (PDA-IE) was a clinically relevant disease with a high morbidity and mortality due to missing therapeutic options before the antibiotic era (Table 1). Mortality in patients with a PDA was reported with up to 4%, in the majority (up to 45%) due to an often chronic PDA-IE.[3,18] Since that time, morbidity and mortality of a PDA declined substantially and cases of PDA-IE have become very rare (<1%).[11] Nevertheless, the only prospective study on the incidence of PDA-IE highlighted a different trend toward higher incidence (up to 4.8/1000 patients treated in a pediatric cardiac center), probably associated with a different health care system.[19]

Therefore, some controversy exists regarding the need for routine closure of a silent or hemodynamic irrelevant PDA for the sole purpose of eliminating the risk of PDA-IE.[1,37] In fact, the development of PDA-IE seems to be more frequent in patients with a hemodynamic relevant PDA,[3-15,18,19] while only anecdotic cases of PDA-IE in a hemodynamic irrelevant PDA are reported.[11,16,24,29,38,39] Only few reports of a PDA-IE in young infants have been published,[15,19,29,39] but due to the increasing number of very low birth weight preterms, where a PDA is a frequent finding, this infective complication has to be kept in mind.

A PDA-IE was previously defined by the presence of a PDA associated to typical vegetation (echocardiography guarantees enough imaging quality for the diagnosis[20]) or positive blood cultures.[37] In accordance to our *S. aureus* bacteremia, bacterial pathogens for PDA-IE are mainly *Streptococcus spp.*, *Staphylococcus spp.*,

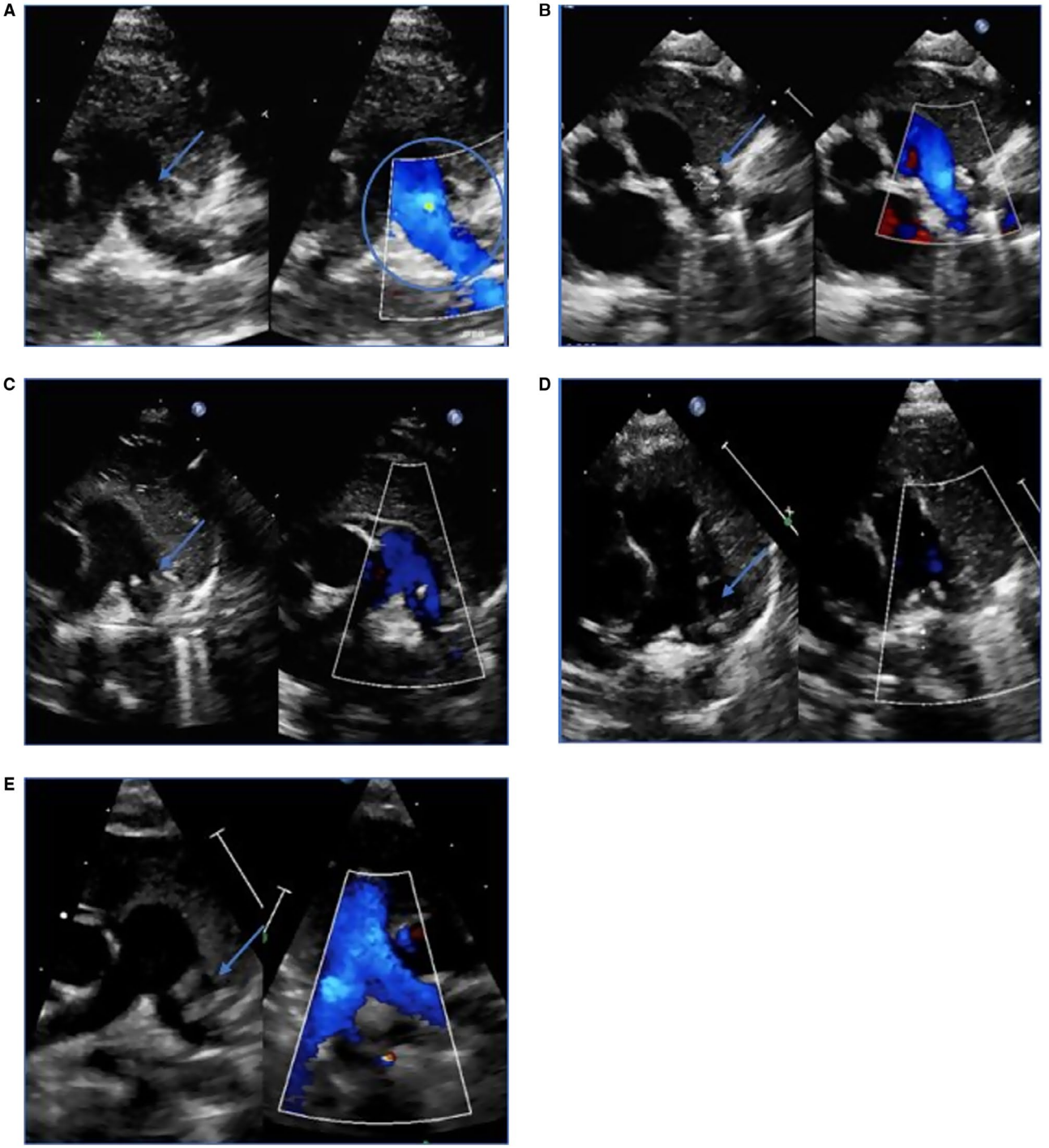

FIGURE 1 Two-dimensional transthoracic echocardiographic long-axis view of the pulmonary arteries and nonpatent ductus arteriosus demonstrating vegetation's evolution (arrow) in dimension and echogenicity at admission (A) 8 × 3 mm; week 1 (B) 8 × 3 mm; week 2 (C) 5 × 4 mm; week 4 (D) 5 × 3 mm; week 9 (E) 5 × 3 mm. Figure A shows the turbulent blood flow (circle) in the left pulmonary artery accelerated by a systolic pulse wave Doppler gradient of V_{max} 180 cm/s compared to the right pulmonary artery V_{max} 141 cm/s, figure B-E demonstrated a normalized systolic pulse

and very rarely Gram-negative rods.[4,8,10,11,15,16,18,22,28-30,36,39] Our echocardiographic findings of a hyperechogenic structure in the parasternal short-axis view in the original shunt flow direction of the PDA are also typical findings due to endothelial lesions surrounding the opening of the PDA on the left pulmonary artery as the predisposing pathogenic factor of an IE.[7,12] Therefore, even if we were not able to determine a residual PDA shunt flow on echo in our patient, the broad diagnostic workup including total body MRI, abdominal ultrasound, CSF, and urine sampling performed to exclude other infectious sources, our diagnosis of a pulmonary

TABLE 1 Review of pediatric and adult case reports/series with PDA-associated infective endocarditis

Author	Ref.	Year	Cnt.	N°	Age	Sex	Diagnosis	Septic embolism	Silent	Symptoms	Pathogen	Therapy	Sur.
Rauchfuss	19	1859	DE	4	1-4 w	3 F 1 M	PDA-IE PA		—	Septic shock	—	Autoptic diagnosis	n
Weinberg	18	1903	DE	1	37 y	F	PDA-IE Ao		—	HF, sepsis	—	Autoptic diagnosis	n
Hart	18	1904	DE	2	23 y	1 M 1 F	PDA-IE PA		—	—	—	Autoptic diagnosis	n
Sommer	18	1910	UK	1	45 y	F	PDA-IE PA		—	—	—	Autoptic diagnosis	n
Hamilton	18	1914	US	1	19 y	F	PDA-IE PA		—	—	Pneumococci	Autoptic diagnosis	n
Terplan	18	1924	–	1	25 y	F	PDA-IE PA/Ao		—	—	*Streptococcus viridans*	Autoptic diagnosis	n
Bedfrot	18	1924	UK	1	20 y	M	Isolated PDA-IE		—	—	—	Autoptic diagnosis	n
Schlaepfer	18	1926	US	1	8 y	M	PDA-IE PA		n	HF, sepsis	*S. viridans*	Autoptic diagnosis	n
Adams	21	1946	US	1	—	—	PDA-IE PA		—	—	—	Penicillin	y
Dammann	22	1946	US	1	—	—	PDA-IE PA		—	—	*S. aureus*	—	y
Vargas-Barron	12	1985	MX	1	9 y	M	PDA-IE PA		n	Fever, anorexia	—	Antibiotics; closure	y
Ciliberto	23	1986	IT	1	30 y	F	PDA-IE PA		n	HF	—	Antibiotics; closure	y
Rivera	9	1997	BR	1	7 y	F	PDA-IE PA		n	Fever	—	Antibiotics; closure	y
Yanýk	8	1999	TR	1	14 y	M	PDA-IE PA		n	HF, fever	*S. viridans*	Penicillin G/gentamicin	y
Parthenakis	16	2000	GR	1	18 y	F	PDA-IE PA		y	Fever	*S. viridans*	Antibiotics; closure	y
Kouris	10	2003	GR	1	43 y	F	PDA-IE;	Lung	n	Fever, HF, cough	*S. viridans*	Penicillin G/gentamycin; closure	y
Flapper	17	2003	AU	1	57 y	F	PDA-IE Ao	Brain spleen	y§	Fever	—	Gentamicin/vancomycin	y
Ozkokeli	24	2004	TK	1	27 y	F	PV + PDA-IE		y	—	—	—	y
Sadiq	36	2004	PK	14	<16 y	10 F 4 M	PDA-IE PA		n	Fever, HF, chest pain, anorexia	*S. viridans S. aureus*	Penicillin G/gentamycin (Vancomycin); closure	y
Bilge	11	2004	US	1	11 y	F	PDA-IE PA	Lung	y	Fever, fatigue	*S. viridans*	Penicillin G/gentamycin; closure	y
Kadakia	25	2004	US	1	25 y	M	PDA-IE PA	Lung	y	Cough, fever	—	—	y
Lankipalli	7	2005	US	1	64 y	F	PDA-IE PA		n	Fever, HF, fatigue	*Gemella species*	Vancomycin/gentamicin; closure	y
Celebi	39	2007	TK	1	2 m	—	—		y	—	—	—	y
Onji	6	2007	JP	1	49 y	F	PDA-IE PA	Lung	n	Sepsis	—	—	y
Choi	26	2008	KR	1	49 y	F	PDA-IE PA	Lung	n	Fever, anorexia	—	penicillin G/gentamycin; closure	y
Grover	15	2008	UK	2	2 w	1 M	PDA-IE PA		n	Fever	Coagulase-negative Staphylococci	Vancomycin/rifampicin	y
					4 w	1 F						Vancomycin/cefotaxime	

(Continues)

TABLE 1 (Continued)

Author	Ref.	Year	Cnt.	N°	Age	Sex	Diagnosis	Septic embolism	Silent	Symptoms	Pathogen	Therapy	Sur.
Bathoorn	[5]	2009	NL	1	62 y	F	PDA-IE PA	Lung	n	Chest pain, fever, anorexia	—	Antibiotics, closure	y
Matsukuma	[27]	2011	JP	1	32 y	M	PDA-IE PA	Lung	n	Fever	—	Antibiotics; IE resection; closure	y
Navaratnarajah	[28]	2011	UK	1	34 y	M	PDA-IE PA	Lung	n	Fatigue, anorexia	*S. viridans*	Antibiotics	y
Ferreira	[29]	2011	PT	1	4 m	M	PDA-IE PA bronchitis		y	Fever; sepsis	*Klebsiella pneumoniae*	Antibiotics; closure	y
Sugimura	[4]	2013	JP	1	63 y	F	PDA-IE PA		n	Fever	*Pseudomonas aeruginosa*	Antibiotics; closure;	y
Malviya	[13]	2016	IN	1	7 y	F	PDA-IE PA		n	Anorexia; fever	—	Antibiotics; closure	n
Miraclin	[30]	2017	IN	1	—	—	PDA-IE PA	Skeleton	n	—	*Abiotrophia defectiva*	Penicillin G/gentamycin; closure	y

Notes: —, unknown; &, vegetation in PDA only; §, nonpatent-PDA. Ref., reference; Cnt., Country in ISO country code (GE: Germany, UK: United Kingdom; US: USA; IT: Italy; BR: Brasil; GR: Greece; AU: Australia; TK: Turkey; PK: Pakistan; JP: Japan; KR: Croatia; PT: Portugal; IN: Indonesia); N°, number of cases; Age in, y (years), m (months), w (weeks); Sex, F = female, M = male; Sur., Survival; PDA-IE, PDA associated infective endarteritis; PA, pulmonary artery; Ao, aorta; SPE, septic pulmonary embolismsm; PV, pulmonary valve; HF, heart failure.
Further cases without clinical details: 1916 [31]; 1948 [32]; 1952 [33]; 1973 [34]; 1986 [20]; 2006 [35]; 2010 [14].

endarteritis remains. The continuous diminishment of the vegetation during the 6-week lasting antibiotic therapy supports our hypothesis. One other case of an infective endarteritis associated with a nonpatent remnant of a ductus arteriosus was reported, but the vegetation was on the aortal side of the former PDA, resulting in an infective aortitis with systemic septic embolism.[17]

According to our literature review (Table 1),[4-36] the typical presentation of a PDA-IE is characterized by prolonged fever (for weeks or even months), sometimes associated to clinical signs of an hemodynamic relevant PDA (fatigue, heart failure, anorexia) or of complications of a PDA-IE such as septic pulmonary or systemic embolisms. Most case reports include patients with an isolated PDA, not associated with other types of CHD or previous cardiac surgery, except one case,[24] where the PDA-IE involves the pulmonary valve. As in the majority of case reports on PDA-IE,[4-36] the origin of the bacteremia was unclear in our patient. Whether the mild redness of the umbilicus before hospital admission was a skin infection and therefore responsible for bacterial entrance remains open. In the neonatal population, transient bacteremia may occur especially in hospitalized preterms due to vascular access as a potential entry site,[15] which we could not find in our infant.

The functional closure of PDA starts directly after birth and the anatomical closure concludes at 10 days of age.[40] The closing mechanism of PDA was clarified by the discovery of prostaglandins in 1936.[40] Previously, Morgagni hypothesized a mechanical compression associated to the lack of circulating blood, while Virchow believed the PDA would close due to thrombus formation.[41] A thrombus formation in the PDA was recently presented by Ciliberti,[42] while Rauchfuss,[19] in 1859, describes four fatal cases of neonates with a thrombotic closure of the PDA associated to blood stream infection. Interestingly, the autoptic reports documented an infected thrombotic formation, which would continue into the pulmonary artery affected by an endarteritis.[19] These findings are in line with our echocardiographic images and with the clinical presentation of our patient. Whether the thrombus formation itself serves as the prerequisite of PDA-IE or the hemodynamic alteration of the endothelial surface surrounding the PDA opening of the LPA remains unclear.

Since the large elastic arteries are generally thought to be resistant to bacterial infection, an abnormal vessel wall anatomy is thought to be a predisposition. In fact, in "classical" PDA-IE the vegetation develops at the end of the PDA due to the Venturi effect,[13] while microscopic tears of the intima resulting from mechanical strain turn the endothelium to a status susceptible for infections that could lead to subsequent thrombosis.[28]

Therefore, two hypotheses for the development of PDA-IE in our patient may be distinguished: *first*, the thrombotic formation in the PDA preceded the infection and the inflammation deriving from the thrombus acted as substrate for the formation of the vegetation; *second*, the spontaneous PDA obliteration was delayed (but preceded the hospital admission) and led to endothelium inflammation, resulting in higher risk for infection and subsequent thrombotic processes, which were the only sign left after successful clearing of the bacteremia.

4 | CONCLUSION

An infective PDA-IE is a rare, but life-threating condition, which may possibly appear even in patients with a recently closed PDA. Increasing awareness for this infective complication in neonates is advised. A possible underreporting of this clinical entity in neonatal patients with a bacteremia is possible. Echocardiography is not invasive, and its integration in the diagnostic workup of young febrile infants with bacteremia without source should be discussed, especially if a new heart murmur develops.

CONFLICT OF INTEREST

All authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Design of the study, data collection/analysis, drafting/approval of article: Alessia Callegari
Data collection, critical revision/approval of article: Barbara Burkhard, Walter Knirsch
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