

# Association Between Childhood Migraine and History of Infantile Colic

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INFANTILE COLIC IS A COMMON CAUSE of inconsolable crying during the first months of life. According to criteria by Wessel, it is usually diagnosed by crying and fussing for more than 3 hours per day, more than 3 days per week, and for more than 3 weeks in an otherwise healthy and well-fed infant.<sup>1</sup> The pathogenesis and the age-specific presentation of colic are not well understood. Infantile colic is usually interpreted as a pain syndrome and may be multifactorial.<sup>2</sup> Allergy to cow's milk proteins, intestinal hormone anomalies, parental factors, and central nervous system dysregulation have been suggested as etiologies.<sup>3</sup> The gastrointestinal tract has been suspected because of the infant's apparent abdominal discomfort, and many thera-

For editorial comment see p 1636.



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[www.jamanetworkcme.com](http://www.jamanetworkcme.com)  
 and questions on p 1638.

**Importance** Infantile colic is a common cause of inconsolable crying during the first months of life and has been thought to be a pain syndrome. Migraine is a common cause of headache pain in childhood. Whether there is an association between these 2 types of pain is unknown.

**Objective** To investigate a possible association between infantile colic and migraines in childhood.

**Design, Setting, and Participants** A case-control study of 208 consecutive children aged 6 to 18 years presenting to the emergency department and diagnosed as having migraines in 3 European tertiary care hospitals between April 2012 and June 2012. The control group was composed of 471 children in the same age range who visited the emergency department of each participating center for minor trauma during the same period. A structured questionnaire identified personal history of infantile colic for case and control participants, confirmed by health booklets. A second study of 120 children diagnosed with tension-type headaches was done to test the specificity of the association.

**Main Outcomes and Measures** Difference in the prevalence of infantile colic between children with and without a diagnosis of migraine.

**Results** Children with migraine were more likely to have experienced infantile colic than those without migraine (72.6% vs 26.5%; odds ratio [OR], 6.61 [95% CI, 4.38-10.00];  $P < .001$ ), either migraine without aura ( $n = 142$ ; 73.9% vs 26.5%; OR, 7.01 [95% CI, 4.43-11.09];  $P < .001$ ), or migraine with aura ( $n = 66$ ; 69.7% vs 26.5%; OR, 5.73 [95% CI, 3.07-10.73];  $P < .001$ ). This association was not found for children with tension-type headache (35% vs 26.5%; OR, 1.46 [95% CI, 0.92-2.32];  $P = .10$ ).

**Conclusion and Relevance** The presence of migraine in children and adolescents aged 6 to 18 years was associated with a history of infantile colic. Additional longitudinal studies are required.

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pies target it.<sup>2</sup> Although benign and self-limited, colic may cause stress in parents and has been reported to lead to shaken baby syndrome.<sup>4</sup>

Migraine is one of the most common causes of primary headaches in children.<sup>5,6</sup> Diagnostic criteria for pediatric migraine have been established by the *International Classifica-*

*tion of Headache Disorders* (Second Edition Revised) (*ICHD-II*).<sup>7</sup> Several migraine variants and childhood periodic syndromes that are common precursors of migraine have been described<sup>7</sup> including abdominal migraine.<sup>8</sup> The 2 major subtypes of migraines are those without and those with aura.

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Tension-type headaches are relatively common in childhood.<sup>9</sup> The headache is bilateral with a pressing or band-like quality of low to moderate intensity. Children with tension-type headaches show an increased pain sensitivity compared with children without tension-type headaches.<sup>10-12</sup> Headache transformation between migraine and tension-type headache is known to occur.<sup>13</sup> Cluster headaches, trigeminal autonomic cephalalgias, and other primary headaches are rare in the pediatric population.<sup>14</sup>

An association between these 2 pain syndromes, colic and migraine, has been proposed but not well studied. We investigated the possible association between migraine and colic in a case-control study. An additional case-control study of children with tension headaches was performed to examine the specificity of any association of infantile colic with migraine.

## METHODS

### Enrollment

We performed a case-control study of consecutive children diagnosed as having primary headaches in 3 European tertiary care hospitals (Robert Debré, Paris, France; Sacco, Milan, Italy; and Santa Maria della Misericordia, Udine, Italy) between April 2012 and June 2012. Written informed consent was obtained from parents and assent from the children. The institutional review boards at each center approved the study protocol.

### Eligibility

We identified new patients aged 6 to 18 years presenting to the emergency department (ED) who were diagnosed with primary headaches by a pediatric neurologist. Control participants were children in the same age range who visited the ED of each participating center for a minor trauma on every Monday from 9:00 AM to 5:00 PM. Children with a personal history of recurrent headaches were excluded from the control group.

### Diagnostic Classification of Headache

For this study, primary headache was classified according to *ICHD-II* crite-

ria<sup>7</sup> (eBox 1, available at <http://www.jama.com>). Only children with migraine and tension-type headache were included. Those with cluster headache, trigeminal autonomic cephalalgias, and other primary headaches were excluded. Patients with a definite diagnosis of migraine, regardless of the presence of concurrent tension-type headache, were classified into the migraine group. If children exhibited distinct episodes of migraine without aura and of migraine with aura, they were allocated to the migraine with aura subgroup for further analysis.

### Data Collection Procedures

**Parent Interview.** Parents were asked to complete a structured questionnaire to determine the patient and family history of infantile colic, defined according to the criteria by Wessel.<sup>1</sup> Parents completed a criteria-based questionnaire<sup>1</sup> followed by the investigators assigning a diagnosis if the criteria were met. The questionnaire also sought demographic and medical information (eBox 2). Physicians and parents were informed that the aim of the study was to explore the potential association between primary headaches and pain (eg, abdominal, muscular), occurring at any developmental age. A number of distractor questions were included in the questionnaire. Parents were interviewed together when they were both present at the ED visit. The pediatric neurologist asked parents to participate in the study only after the type of primary headache was established and without knowledge of a diagnosis of colic. These physicians then interviewed parents to complete the questionnaire. The same questionnaire was given to parents of children in the control group by the ED physician who cared for their child.

**Health Booklet Review.** The physicians also examined each child's personal national health booklet (*carnet de santé* [French version]; *libretto sanitario* [Italian version]). These booklets are mandatory for each child. They are given to parents soon after birth and contain medical data from birth to adult-

hood. The booklets have pages dedicated to different developmental stages. Each sheet is completed by the physician at each clinical visit. The recorded data are the date of consultation, age, major clinical findings, diagnosis, and therapy. Only physicians may write diagnoses in the health booklet. The physicians who participated in the study completed the questionnaire by using the health booklet to retrieve accurate medical information on gestational age, birthweight, and coexisting chronic medical conditions. The diagnosis of colic in the health booklet was also recorded to analyze potential discrepancies between the diagnosis based on Wessel<sup>1</sup> criteria and information recalled by parents, vs the diagnosis recorded in the health booklet.

### Statistical Analysis

The study size was calculated as described in a previous report,<sup>15</sup> to allow the identification of a 4-fold increased risk of migraines when there was a history of infantile colic. Based on local data, a frequency of infant colic of 40% was expected in our population. A sample size of 136 patients with migraine was calculated with a power of 80% at the .05 level of significance (2-sided). Based on the number of migraines diagnosed at each center during a standard month, we estimated the total inclusion period at 3 months. The number of needed control participants was calculated based on the average number of consultations for minor trauma at the ED of each center over the same period.

The primary outcome measure was the difference in the prevalence of infantile colic between children with and without a diagnosis of migraine. Differences in prevalence of colic between children with and without tension-type headaches were assessed to examine the specificity of the association.

We selected candidate predictors of infantile colic based on the results of previous studies and biological plausibility. The following clinical and biological data were obtained from health booklets and parental interviews: demo-

graphic data (age, sex, consanguinity, gestational age at birth, and birth weight), presence of infantile colic in first-degree relatives, presence and diagnosis of primary headache in first-degree relatives, breastfeeding, coexisting medical conditions, and if the child had repeated a grade at school. For case participants, we also recorded the age at which the first manifestations of headache appeared and the frequency and characteristics of painful episodes. Treatments for primary headaches and their duration were also scored. Overall, missing data represented 0.9% of data and never concerned the diagnosis of infantile colic.

Categorical variables were compared using  $\chi^2$  analysis and continuous variables were compared using the Mann-Whitney test. The chosen level

of significance was .05 (2-sided). Bivariable and multivariable analyses were carried out to identify factors associated with migraines and tension-type headaches. Only variables that were significant in the bivariate analysis at the 20% nominal level (gestational age, the presence of infantile colic, the presence of infantile colic and primary headaches in first-degree relatives, formula feeding) were considered in the multivariable analysis based on logistic regression. The presence of recurrent abdominal pain during childhood and the presence of sleep disorders could be manifestations of colic or migraine and therefore were not included in the analysis. Results were adjusted for age considered as a continuous variable. Odds ratios (ORs) and 95% confidence intervals were calculated.

To determine whether infantile colic was associated with a specific migraine subgroup, we performed the same analyses considering patients with migraine without aura and migraine with aura separately. Furthermore, to study the possible bias due to the inclusion in the control group of younger children who might not yet have developed migraine and were thus erroneously considered as control participants, we performed a subgroup analysis for patients with migraine and control participants aged either 6 to 12 years or 12 to 18 years. Statistical analyses were performed using SAS statistical software version 9.2 (SAS Institute).

## RESULTS

A total of 328 patients (208 children who experienced migraine [142 with-

**Table 1.** Patient Characteristics

Child Characteristics	Migraine Group <sup>a</sup> (n = 208)	Control Group <sup>a</sup> (n = 471)	P Value	Tension-Type Headache (n = 120) <sup>a</sup>	P Value <sup>b</sup>
Boys, No.	122	280	.85	65	.30
Girls, No.	86	191		55	
Age at evaluation, median (IQR), y	10.1 (8.2-13.7)	9.0 (7.0-12.0)	.001	10.1 (8.0-12.0)	.01
Aged 6-11.9 y	129 (62.0)	337 (71.5)		84 (70.0)	
Aged 12-18 y	79 (38.0)	134 (28.5)		36 (30.0)	
Gestational age at birth, median (IQR), wk	40 (38-40)	40 (38-40)	.25	40 (39-40)	.02
Birth weight, median (IQR), g	3345 (3000-3640)	3310 (2980-3640)	.61	3370 (3005-3595)	.56
Breastfeeding			.002		.001
Exclusive	106 (50.9)	295 (62.6)		55 (45.8)	
Mixed	44 (21.2)	70 (14.9)		32 (26.7)	
Formula feeding	58 (27.9)	106 (22.5)		33 (27.5)	
<b>Conditions Reported in Infancy and Childhood</b>					
Diagnosis of infantile colic	151 (72.6)	125 (26.5)	<.001	42 (35.0)	.07
Recurrent abdominal pain during childhood	38 (18.3)	22 (4.7)	<.001	13 (10.8)	.01
Coexisting chronic medical conditions <sup>c</sup>	16 (7.4)	39 (8.3)	.80	8 (6.6)	.56
Repeated a grade in school	12 (5.8)	23 (4.9)	.63	3 (2.5)	.26
Sleep disorders <sup>d</sup>	20 (9.6)	9 (1.9)	<.001	14 (11.7)	<.001
Family history					
Parental consanguinity	7 (3.4)	25 (5.3)	.27	1 (0.8)	.03
Primary headache in first-degree relatives	165 (79.3)	157 (33.3)	<.001	79 (65.8)	<.001
Migraine with aura <sup>e</sup>	38 (23)	28 (17.8)		17 (21.5)	
Migraine without aura <sup>e</sup>	89 (54)	49 (31.2)		41 (51.9)	
Tension-type headache <sup>e</sup>	38 (23)	77 (49)		21 (26.6)	
Other types <sup>e</sup>	0	3 (0.6)		0	
Infantile colic in first-degree relatives	53 (25.5)	47 (10)	<.001	26 (21.7)	<.001

Abbreviation: IQR, interquartile range.

<sup>a</sup>Data are reported as No (%) of participants unless otherwise indicated.

<sup>b</sup>P values compare tension-type headache with control participants.

<sup>c</sup>The most common chronic medical conditions were asthma, diabetes, recurrent urinary tract infections, and sickle cell anemia.

<sup>d</sup>As diagnosed by *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) criteria.

<sup>e</sup>Headache subtypes are among first-degree relatives with primary headache.

out aura and 66 with aura] and 120 diagnosed with tension-type headaches) and 471 control participants were included in the study. Only 1 family in the primary headache group refused consent. Fifty-five children (10.5%) were excluded from the control group for recurrent headaches. None of the parents of children in the control group refused participation.

The baseline clinical characteristics of patients are shown in TABLE 1. No unequivocal cases of infantile colic were encountered because the histories were

either definitely positive or negative in all patients and were always in agreement with the diagnoses recorded in the personal health booklet. The booklet was available for 325 of the 328 children (99.1%) in the primary headache group and for 467 of the 471 children (99.2%) in the control group. All children for whom parents reported a history of colic had a diagnosis of infantile colic recorded in their health booklets. None of the children for whom parents did not recall any colic had a diagnosis of colic recorded in the health booklet.

In children with migraine, 72.6% (151/208) reported infantile colic. In the migraine with aura group, the prevalence of colic was 69.7% (46/66 children), and in the migraine without aura group the prevalence was 73.9% (105/142 children). In the tension-type headache group, the prevalence was 35.0% (42/120 children), and in the control group, the prevalence was 26.5% (125/471 children). The characteristics of headaches in children diagnosed with migraine and tension-type headache are presented in TABLE 2.

The logistic regression results considering diagnosis of colic using the parental interview and the health booklet are presented in TABLE 3 and showed a significant association between infantile colic and migraine (72.6% vs 26.5%; OR, 6.61 [95% CI, 4.38-10.00];  $P < .001$  by parent report; 72.6% vs 26.3%; OR, 6.68 [95% CI, 4.40-10.13];  $P < .001$  using health booklets). This association was not found for infantile colic and tension-type headache (35.0% vs 26.5%; OR, 1.46 [95% CI, 0.92-2.32];  $P = .10$  by parent report; 35.0% vs 26.3%; OR, 1.48 [95% CI, 0.93-2.36];  $P = .10$  using health booklets). No statistically significant differences were observed by center for any of the variables included in the logistic regression. The presence of primary headaches in first-degree relatives, as well as mixed formula feeding, were all significantly associated with either migraine or tension-type headache.

The subgroup analysis for migraine subtypes confirmed the association between infantile colic and either migraine without aura (73.9% vs 26.5%; OR, 7.01 [95% CI, 4.43-11.09];  $P < .001$ ) or migraine with aura (69.7% vs 26.5%; OR, 5.73 [95% CI, 3.07-10.73];  $P < .001$ ; eTable 1). The subgroup analyses for age (6 to 12 and 12 to 18 years) confirmed a significant association between infantile colic and migraine in both age groups (eTable 2).

When comparing migraine characteristics in children with or without a history of infantile colic, a pulsating quality of pain was more frequently reported in the infantile colic subgroup ( $P = .003$ ; TABLE 4).

**Table 2.** Headache and Associated Symptoms in Patients With Pediatric Migraine and Patients With Tension-Type Headache<sup>a</sup>

Characteristics	Migraine Group (n = 208)	Tension-Type Headache Group (n = 120)
Age at first manifestations of headache, median (IQR), y	7.0 (6.0-9.1)	6.9 (5.1-9.0)
Time since first manifestations of headache, median (IQR), y	2.4 (1.0-4.2)	2.9 (1.0-4.0)
Migraine attacks per mo, median (IQR), No.	2 (1-4)	3 (1-8)
Prescription of preventive therapy	24 (11.5)	10 (8.3)
Pain during migraine attacks reported		
Unilateral location	99 (47.6)	
Pulsating quality	173 (83.2)	
Aggravation by or causing avoidance of routine physical activity	169 (81.3)	
Nausea	119 (57.2)	
Vomiting	96 (46.2)	
Phonophobia	163 (78.4)	
Photophobia	165 (79.3)	
Aura	66 (31.7)	
Visual symptoms	56 (84.8)	
Sensory symptoms	8 (12.1)	
Motor symptoms	2 (3.0)	

Abbreviation: IQR, interquartile range.

<sup>a</sup>Data are reported as No (%) of participants unless otherwise indicated.

**Table 3.** Multivariable Odds Ratios of Primary Headaches by Primary Source for Infantile Colic Diagnosis

	Outcome, OR (95% CI)			
	According to Parent Interview		According to Health Booklet	
	Migraine	Tension-Type Headache	Migraine	Tension-Type Headache
Presence of infantile colic	6.61 (4.38-10.00)	1.46 (0.92-2.32)	6.68 (4.40-10.13)	1.48 (0.93-2.36)
Primary headache in first-degree relatives	6.64 (4.30-10.25)	3.65 (2.34-5.71)	6.98 (4.50-10.81)	3.84 (2.45-6.02)
Mixed formula feeding	1.65 (1.09-2.48)	2.23 (1.44-3.44)	1.66 (1.10-2.51)	2.25 (1.45-3.49)
Gestational age at birth (per 1 week)	1.04 (0.93-1.15)	1.23 (1.07-1.41)	1.05 (0.94-1.16)	1.24 (1.10-1.43)
Infantile colic in first-degree relatives	1.10 (0.65-1.88)	1.37 (0.77-2.44)	1.04 (0.61-1.78)	1.29 (0.72-2.32)

Abbreviation: OR, odds ratio.

**COMMENT**

We aimed to investigate the possible association of infantile colic with pediatric migraine. For children with migraine, the odds of having had colic as an infant were increased. For children with tension headache, the odds of having had colic were not significantly different from the odds for control participants, confirming the specificity of the association.

An association between infantile colic and migraine has been suggested in sporadic reports<sup>16</sup> and in a longitudinal study of hyperreactive infants, ie, infants exhibiting irritability, infantile colic, and crying bouts during their first months of life.<sup>17</sup> In this study, an increased prevalence of migraine was found among 102 hyperreactive children followed up for 10 years compared with control participants (52.9% vs 15%). A case-control study of 29 children with migraine and 29 control participants with epilepsy found that 15 children with migraine (52%) and 6 control participants (20%) had a history of infantile colic<sup>15</sup> and children with migraine were 4 times more likely to have a history of infantile colic (95% CI, 1.1-15.0;  $P = .02$ ). Children with a history of infantile colic ( $n = 21$ ) were more likely to have a family history of migraine than those without colic (18/21 vs 10/37;  $P = .001$ ). In another retrospective study focusing on sleep disorders in children with headaches,<sup>12</sup> a history of colic was also more likely in children with migraine than in headache-free control participants (38.4% vs 26.9%). Maternal migraine has been recently reported to be associated with an increased risk of infantile colic,<sup>18</sup> suggesting that colic may be an early-life manifestation of migraine.

In our study, the association with infantile colic was significant for migraine without aura as well as migraine with aura with similar odds ratios, suggesting a common pathophysiology of migraine and infantile colic. The link between infantile colic and migraine could be based on a pathogenetic mechanism common to migraine without aura and also migraine with aura. We found that among migraine characteristics, only pulsatile pain was more frequent in children with a history

**Table 4.** Headache and Associated Symptoms in Patients Diagnosed With Migraine, Comparing Children With and Without History of Infantile Colic<sup>a</sup>

	Infantile Colic <sup>a</sup>		P Value
	No (n = 57)	Yes (n = 151)	
Age at first manifestations of migraine, median (IQR), y	8.0 (6.0-10.0)	7.0 (5.5-9.0)	
Migraine attacks per mo, median (IQR), No.	2 (1-4)	2 (1-3)	
Unilateral location	21 (36.8)	78 (51.6)	.06
Pulsating quality	40 (70.2)	133 (88.1)	.003
Aggravation by or causing avoidance of routine physical activity	46 (80.7)	123 (81.5)	>.99
Nausea	32 (56.1)	87 (57.6)	.88
Vomiting	28 (49.2)	68 (45.0)	.64
Phonophobia	47 (82.4)	116 (76.8)	.45
Photophobia	46 (80.7)	119 (78.8)	.85
Aura	20 (35.1)	46 (30.5)	.62
Prescription of preventive therapy	5 (8.7)	19 (12.5)	.60

Abbreviation: IQR, interquartile range.

<sup>a</sup>Data are reported as No (%) of participants unless otherwise indicated.

of infantile colic than among children with migraine but without infantile colic. Infants with colic might experience a similar sensitization of the perivascular nerve terminals in the gut, although this hypothesis needs to be tested. Molecules known to be involved in the modulation of sensory activity, such as calcitonin-gene-related peptide (CGRP) could also be involved. CGRP is released during migraine episodes<sup>19</sup> and CGRP antagonists are efficacious pain management agents. CGRP is also potentially involved in the pathogenesis of abdominal pain by inducing the neurogenic inflammation of sensory neurons in the gut.<sup>20</sup>

Our study has some limitations. First, it is a case-control study. However, a prospective longitudinal study—from birth until adolescence—would be difficult to perform. To serve as a proof of concept, we chose to perform a multicenter study that included a sufficient number of patients to increase the generalizability of our findings.

Second, we relied on the diagnosis of infantile colic by review of personal medical records and by parental interview. The possibility of recall bias for an event many years previously is possible. However, parents vividly remembered the infantile colic episodes. Furthermore, parents were asked to retrieve information regarding recurrent pain at any developmental age, therefore not focusing only

on a positive history of infantile colic which could have caused a potential bias. A response bias could have been induced by interviewing parents of patients by pediatric neurologists and parents of control participants by ED physicians. However, both pediatric neurologists and ED physicians were pediatricians. We thought that the answers would be less subject to bias when the questionnaire was filled out by the same physician who cared for the child. Furthermore, waiting for another clinician would have tired parents and potentially biased their answers. Also, the analysis performed using only booklet exposure information was less subject to recall bias than using information by parental interview.

Third, difficulties in the diagnosis of primary headaches in children are well known and include changes in phenotype with age and the coexistence of migraines and tension-type headaches.<sup>5,13</sup> The primary objective of the study was to explore the association between infantile colic and migraine: only 3 patients met the criteria for both migraine without aura and tension-type headache at the same time and were classified in the migraine without aura group. We also performed a statistical analysis for age-based subgroups to explore a potential age-related diagnostic bias. Infantile colic and migraine were signifi-

cantly associated in both age subgroups. Finally, children included in this study presented with acute headache to the ED and were subsequently seen by a pediatric neurologist. Children with milder or less recurrent headaches perhaps do not present to the ED. Children included in the study therefore might not be representative of all children with migraines or tension headaches.

The treatment of infantile colic includes drugs, nutritional changes, behavioral strategies, and alternative medicines.<sup>21,22</sup> There is scientific evidence that casein hydrolysate formula is useful for infants with colic because of the potential role of allergies to cow's milk proteins in such infants.<sup>23</sup> The increased exposure to cow's milk proteins among formula-fed infants could partly explain our finding of a significant association between formula feeding and migraine. The other possibility is that breastfeeding protects children from migraine, but this hypothesis has to be confirmed. Favorable results have also been obtained by decreasing the infant's level of stimulation during infantile colic episodes,<sup>24-26</sup> with a calculated beneficial effect size of 0.48 (0.23-0.74).<sup>25,27</sup>

Decreased stimulation and relaxation techniques are also useful interventions for the treatment of migraine attacks.<sup>28,29</sup> No other therapies have been proven effective in randomized clinical trials for infants with infantile colic.<sup>21</sup>

A significant contribution to migraine treatment has been made by the advent of the triptans, which are 5HT<sub>1B/D</sub> receptor agonists. These drugs are effective against acute attacks of migraine and abdominal migraine.<sup>30</sup> Although it is currently difficult to imagine that clinical trials will be conducted with such off-label drugs for the treatment of a benign condition such as infantile colic, it should be noted that infantile colic causes pain in infants and high levels of stress in parents. In one report, an infant with colic experienced improvement after starting antimigraine (cyproheptadine) therapy.<sup>16</sup> Additional study is required before considering antimigraine treatment as an option for infant colic.

The presence of migraine in children and adolescents aged 6 to 18 years was associated with a history of infantile colic. Longitudinal studies are needed to explore the association further.

**Author Contributions:** Dr Titomanlio had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Romanello, Alberti, Titomanlio.

**Acquisition of data:** Romanello, Spiri, Marcuzzi, Zanin, Riviere, Vizeneux, Moretti, Carbajal.

**Analysis and interpretation of data:** Romanello, Zanin, Boizeau, Mercier, Wood, Zuccotti, Crichiutti, Alberti, Titomanlio.

**Drafting of the manuscript:** Romanello, Zanin, Titomanlio.

**Critical revision of the manuscript for important intellectual content:** Romanello, Spiri, Marcuzzi, Zanin, Boizeau, Riviere, Vizeneux, Moretti, Carbajal, Mercier, Wood, Zuccotti, Crichiutti, Alberti, Titomanlio.

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**Study supervision:** Romanello, Spiri, Zanin, Vizeneux, Mercier, Wood, Zuccotti, Crichiutti, Titomanlio.

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**Online-Only Material:** eBoxes 1 and 2 and eTables 1 and 2 are available at <http://www.jama.com>.

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