A 10-year cross-sectional study showed that anti-coagulation therapy was not always of value when treating paediatric cases with septic cerebral venous thrombosis.

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ACTA PÆDIATRICA NURTURING THE CHILD WILEY

ORIGINAL ARTICLE

A 10-year cross-sectional study showed that anti-coagulation therapy was not always of value when treating paediatric cases with septic cerebral venous thrombosis

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Abstract

Aim: Cerebral venous thrombosis (CVT) is a rare complication of ear, nose and throat (ENT) infections. Although recent guidelines recommend the systematic use of anti-coagulation therapy (ACT) in the treatment of these CVT, literature data are scarce. The present study's objective was to determine the value of ACT in achieving recanalisation after thrombosis and its effect on patient outcomes.

Methods: All paediatric patients with CVT and a concomitant ENT infection who attended Lille University Hospital (Lille, France) between January 2012 and December 2021 were retrospectively included.

Results: We included 43 children (63% boys), with a mean age of 4 years. The most frequent infection was mastoiditis (54%). ACT was initiated in 23 patients (53%), one of whom had an intracranial haemorrhage. Partial or full recanalisation was observed in 33 (80%) of the 41 survivors. In patients with no neurological signs and symptoms on admission and in patients with mastoiditis-related CVT, the clinical and radiological outcomes were favourable and did not differ according to the administration of ACT. Likewise, ACT did not appear to influence the recanalisation rate or sequelae.

Conclusion: ACT was not necessary for all patients with mastoiditis-related CVT and those with no neurological signs and symptoms on admission.

KEYWORDS
anti-coagulation, children, infection, intracranial venous thrombosis

1 | INTRODUCTION

Ear, nose and throat (ENT) infections are the most common infectious diseases in children. Up to 83% of children will experience an episode of acute otitis media before 3 years of age.[1] Although most ENT infections are benign, some can be complicated by cerebral venous thrombosis (CVT). The majority of cases of CVT are associated with mastoiditis or meningitis following an ENT infection.[2]

Abbreviations: ACT, anti-coagulation therapy; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; CVT, cerebral venous thrombosis; ENT, Ear, nose and throat; MRI, magnetic resonance imaging; PICU, paediatric intensive care unit.

According to the Canadian Paediatric Ischemic Stroke Registry, the annual incidence of CVT in the general population of children is 0.67 per 100 000.[3] These thromboses can lead to intracranial hypertension, cerebral oedema, venous infarction, intracranial haemorrhage, other brain injuries, neurological sequelae, and even death.[4,5] Pathogens that produce circulating toxins such as *Fusobacterium necrophorum*, which is responsible for Lemierre syndrome, are more likely to cause CVT.[6,7]

Regarding the management of post-infectious CVT, early antibiotic therapy, combined if necessary with surgical management, is recommended by many authors, while anti-coagulation therapy (ACT) is subject to debate.[8] When the present study was initiated, there were no clear criteria in the literature on the introduction of ACT in these patients. French national guidelines were published at the end of the study period in September 2021 and recommended ACT for all patients. However, we feel that the use of ACT in some patients is excessive, given the risk of bleeding. In Rebelo et al.'s literature review, 51 (63.7%) of the 80 paediatric cases with Lemierre syndrome reported between 2002 and 2014 mentioned the use of ACT.[9] Likewise, Wong et al.'s literature review found that ACT was administered in 113 (59%) of 190 patients with mastoiditis complicated by CVT.[10] With ACT, the goal is to recanalise the obstructed blood vessel. Partial recanalisation does not necessarily imply a worse clinical outcome, and several studies have shown that complete recanalisation can be achieved in the absence of ACT. Hence, we decided to evaluate the value of ACT in the management of these complicated ENT infections.[6,10–12]

Thus, the primary objective of the present study was to assess the value of ACT for achieving recanalisation after thrombosis and its effect on the outcomes of patients. The secondary objectives were to describe the adverse events associated with ACT and evaluate the possible influence of the infection site and the symptoms at diagnosis on the clinical and radiological outcomes.

Key notes

- In cases of septic cerebral venous thrombosis (CVT), it is not clear whether anti-coagulation therapy (ACT) is of value and poses a bleeding risk.
- Partial or full venous recanalisation was observed in 80% of cases, including some who had not received ACT.
- ACT did not appear to influence the clinical and radiological outcomes in patients with mastoiditis-related CVT and in patients with no neurological symptoms on admission; one patient suffered a haemorrhagic complication of ACT.

2 | MATERIALS AND METHODS

2.1 | Study design

We conducted a single-centre, retrospective, cross-sectional study at Lille University Hospital (Lille, France) over a 10-year period from 1 January 2012 to 31 December 2021. We included children admitted to a paediatric ward or the paediatric intensive care unit (PICU) after visiting an emergency department for the management of an ENT infection complicated by CVT.

2.2 | Patient selection

Eligible patients were identified by querying our university hospital's electronic medical records with specific codes from the International Classification of Diseases, Tenth Revision (Table S1). Patients were considered for inclusion if they were treated in the paediatric emergency department or PICU with certain main or associated diagnoses. These were acute otitis media, pharyngitis, para or retropharyngeal abscess, sinusitis, mastoiditis, meningitis and CVT.

All the patients were under 18 years of age and had CVT diagnosed by contrast-enhanced MRI or CT and a concomitant ENT infection. The main exclusion criterion was the absence of appropriate brain imaging data for the detection of CVT.

2.3 | Endpoints and definitions

The primary endpoint was venous recanalisation after thrombosis. The secondary endpoints were neurological sequelae, bleeding associated with ACT use and the clinical outcomes as a function of ACT use, the infection site and the presence or absence of neurological signs and symptoms on admission.

Post-infectious CVT was defined as the visualisation on contrast-enhanced MRI or CT of the interruption of flow in one or several venous sinuses of the brain, due to a blood clot.[13,14] The ENT infections were classified into four categories: mastoiditis, meningitis, sinusitis, and pharyngeal abscess. Mastoiditis was defined as the infection of mastoid air cells in a child with a suggestive clinical presentation.[15] Meningitis was defined as the presence of meningeal inflammation on lumbar puncture, with a documented infection.[16] Sinusitis was defined clinically and radiologically as documented congestion of the sinus cavities in a feverish, symptomatic patient.[17] Pharyngeal abscesses included retropharyngeal and parapharyngeal abscess, as diagnosed by visualisation of a collection on contrast-enhanced CT.[18] Inclusion in the ACT group was based on the use of any type of ACT, at a hypocoagulant dose level. Patients were first given unfractionated or low molecular weight heparin and then a vitamin K agonist or a direct oral anti-coagulant.

The extent of the CVT was graded using a standardised, reproducible venous occlusion image score (Figure S1).[19] During follow-up, recanalisation was rated as absent if the involved vessel

was still fully occluded, partial if venous flow was present but the clot persisted, or complete if venous flow had normalised on imaging.

2.4 | Collected data

Patient data were collected retrospectively from electronic medical records. The data included personal and/or family histories of thromboembolic disease or immunodeficiency, the type of ENT infection, the ward to which the patient had been admitted, the administration of ACT if any, and the duration of ACT if administered. The clinical outcome and any neurological sequelae were documented. Laboratory variables recorded at diagnosis included the serum C-reactive protein level, the white blood cell count, and bacteriological data from blood or cerebrospinal fluid cultures and/or surgical samples. The radiological variables collected were the site and extent of the CVT on contrast-enhanced MRI or CT, associated intracranial infectious or ischemic lesions if any, and the recanalisation outcome. Brain imaging datasets obtained on diagnosis and during follow-up were reviewed by a board-certified neuroradiologist, in order to confirm the diagnosis of CVT, specify the site of the clot, grade the venous occlusion image score, and assess the degree of recanalisation during follow-up. When possible, the time to complete recanalisation was documented. If not, the most recent available imaging dataset was used to evaluate the degree of recanalisation. The reviewing neuroradiologist was blinded to the clinical outcome and whether or not ACT had been used.

2.5 | Statistical analysis

The study population was described as a whole and then in two subgroups: ACT or no ACT. Continuous variables were expressed as the median and interquartile range (IQR). Categorical variables were expressed as the frequency and percentage. The recanalisation rates with their 95% confidence intervals were calculated overall and by subgroup. The distribution of variables, including ACT use, venous recanalisation, and outcome, was compared in patients with mastoiditis versus patients with another ENT infectious complication and in patients with versus without neurological signs and symptoms on admission. Groups were compared using a chi-squared test or Fisher's exact test for categorical variables and Student's test or the Mann–Whitney *U* test for continuous variables. The threshold for statistical significance in two-tailed tests was set to $p < 0.05$. The statistical analyses were performed using pvalue.io software (Medistica, Paris, France).[20]

2.6 | Ethics

The study database was registered with the French Data Protection Commission (registration number: DEC 23–033). In line with the French legislation, the patients and their parents were given information about the study and were free to object to the use of their personal medical data for research purposes.

3 | RESULTS

3.1 | Characteristics of the study population

We screened 868 patients and 43 (males: 63%) met all the inclusion criteria. The median [IQR] age was 4 [1.75–9.5] years (Figure 1). The most frequent ENT infections were acute mastoiditis (54%, $n = 23$) and acute sinusitis (23%, $n = 10$). Five patients presented with an underlying risk factor for infection: Crohn's disease requiring immunosuppressive treatment ($n = 1$), DiGeorge syndrome ($n = 1$), and a skull base defect ($n = 3$). Only two children had a documented family history of venous thromboembolic disease. Another child was found to have a heterozygous factor V Leiden mutation. A microorganism was identified in 26 patients (61%). The most frequently detected microorganisms were *Streptococcus intermedius* ($n = 7$), *Streptococcus pneumoniae* ($n = 7$), and *Fusobacterium necrophorum* ($n = 5$) (Table S2). Two or more microorganisms were isolated in four cases.

Thrombosis at two or more sites was observed in 23 of the patients (53%). The median number of thrombosis sites was 2, and the

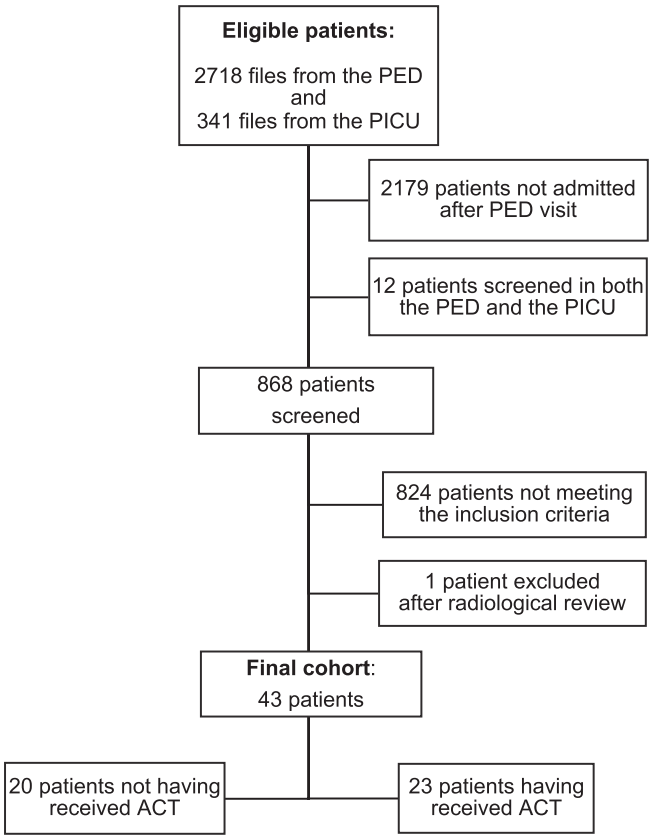

FIGURE 1 Study flow chart. ACT, Anti-coagulation therapy; PED, Paediatric emergency department; PICU, Paediatric intensive care unit.

median [IQR] venous occlusion image score was 2 [1–3]. The most frequently affected sites were the sigmoid sinus (61%, $n=26$), the jugular vein (47%, $n=20$), and the transverse sinus (40%, $n=17$) (Table 1). Three patients presented with a contralateral extension of the thrombosis. Associated empyema was observed in 19 patients (44%).

3.2 | Outcomes

ACT was initiated in 23 (53%) of the 43 patients, for a duration ranging from 2 weeks to 7 months. The median ACT treatment time was 3 months. The two patients with family history of venous thromboembolic disease and the one patient with heterozygous factor V Leiden mutation received ACT.

One patient in the ACT group was diagnosed with an intracerebral hematoma and intracranial hypertension during follow-up, after 5 months of ACT. Two patients died (5%). Among the 41 survivors, we observed complete recanalisation in 16 (39%) and partial recanalisation in 17 (41%). Follow-up brain imaging was not performed for five patients. The last three patients had persistent venous occlusion on the most recent imaging dataset, acquired one, one, and 17 weeks after diagnosis, respectively. Lastly, 92% of the children with follow-up brain imaging data had partial or full recanalisation.

The majority of the patients ($n=29$, 67%) were admitted to the PICU. With regard to the two deaths, a 13-year-old girl died 5 days after admission. The cause was diagnosed as cranial hypertension with brain herniation due to Lemierre syndrome and a brain cerebral abscess. The second patient, an 8-year-old boy, died 15 days after

TABLE 1 Characteristics of the study population ($n=43$).

Variables	*n* or median	% or IQR
Age (years)	4	1.75–9.50
Male sex	27	63%
Family history of venous thrombosis	2	5%
Immunodeficiency or immunosuppressive treatment	5	12%
Initial ear, nose and throat infection		
Mastoiditis	23	54%
Sinusitis	10	23%
Meningitis	7	16%
Pharyngeal abscess	3	7%
Neurological signs or symptoms on admission	17	40%
Empyema	19	44%
Vasculitis	4	9%
C-reactive protein (mg/L) ($n=39$)	221	175–276
White blood cell count (G/L) ($n=30$)	18	11.6–23.6
Thrombosis site		
Sigmoid sinus	26	61%
Internal jugular vein	20	47%
Transverse sinus	17	40%
Superior sagittal sinus	6	14%
Cavernous sinus	6	14%
Superior petrous sinus	3	7%
Straight sinus	2	5%
Inferior sagittal sinus	1	2%
Bilateral thrombosis	3	7%
Number of thrombosis sites	2	1–3
Multiple thrombosis	23	53%
Venous occlusion imaging score	2	1–3
Neurological sequelae ($n=41$)[a]	8	20%
Recanalisation rate (full or partial) ($n=41$)[a]	33	80%
Time to recanalisation (days) ($n=41$)[a]	40	22–116

[a]Number of survivors, including five patients without follow-up imaging.

admission due to venous ischemic lesions caused by widespread thrombosis in the context of bacterial meningoencephalitis.

Eight patients had neurological sequelae after 1 month of follow-up. There were four cases of parenchymal ischemic lesions manifesting themselves as tetraplegia, axial hypotonia, and spastic hemiparesis. Three patients presented with hydrocephaly, resulting in axial hypotonia and pyramidal syndrome. One patient experienced an intracerebral haemorrhage, resulting in hydrocephaly and intracranial hypertension that required cerebrospinal fluid derivation, and with ophthalmoplegia and facial paralysis as sequelae. Seven of these eight patients had neurological signs and symptoms on admission.

3.3 | Group comparison

ACT was administered significantly more frequently to males ($p=0.02$), patients admitted to the PICU ($p=0.02$), and patients with non-otogenic thrombosis ($p=0.04$). There were no associations between ACT use and any of the laboratory or imaging variables (Table 2). The overall (partial and total) recanalisation rate (80%) was not significantly related to the administration of ACT ($p=0.45$).

In patients with no neurological signs and symptoms on admission, mastoiditis was the most frequent infection, and the sigmoid sinus and the internal jugular vein were the more frequent

TABLE 2 Comparison of patients who received ACT and those who did not.

	ACT received ($n=23$)		No ACT ($n=20$)				
Variables	***n/N* or median**	**% or IQR**	***n/N* or median**	**% or IQR**	**OR**	**95% CI**	***p***
Age (years)	7	3–13	3	1–4	NA	NA	0.09
Male sex	18/23	78%	9/20	45%	4.4	1.2–16.6	0.02
Family history of venous thrombosis	2/23	9%	0/20	0%	4.8	0.2–105	0.49
Immunodeficiency or immunosuppressive treatment	3/23	13%	2/20	10%	1.35	0.2–9	1
Initial infection							
Mastoiditis	9/23	39%	14/20	70%	0.28	0.1–1	0.04
Sinusitis	9/23	39%	1/20	5%	12.2	1.4–107.8	0.01
Meningitis	5/23	22%	2/20	10%	2.50	0.4–14.6	0.42
Pharyngeal abscess	0/23	0%	3/20	15%	0.10	0.01–2.2	0.09
Neurological signs or symptoms on admission	13/23	57%	4/20	20%	5.20	1.3–20.5	0.02
Admission to the PICU	19/23	83%	10/20	50%	4.75	1.2–19	0.02
Empyema	12/23	52%	7/20	35%	2.03	0.6–7	0.26
Vasculitis	3/23	13%	1/20	5%	2.85	0.3–30	0.61
C-reactive protein (mg/L) ($n=39$)	230	186–276	215	132–274	NA	NA	0.36
White blood cell count (G/L) ($n=30$)	16	10.8–20	21	15.5–24.5	NA	NA	0.27
Thrombosis site							
Sigmoid sinus	11/23	48%	15/20	75%	0.31	0.1–1.1	0.07
Internal jugular vein	10/23	44%	10/20	50%	0.77	0.2–2.6	0.67
Transverse sinus	12/23	52%	5/20	25%	3.27	0.9–12	0.07
Other	12/23	52%	4/20	20%	4.36	1.1–17.1	0.06
Bilateral thrombosis	3/23	13%	0/20	0%	7.00	0.3–144.2	0.24
Number of thrombosis site	2	1–3	1.5	1–2	NA	NA	0.22
Multiple thrombosis	15/23	65%	8/20	40%	2.80	0.8–9.7	0.10
Venous occlusion imaging score	2	1–3	1,5	1–2	NA	NA	0.43
Neurological sequelae ($n=41$)[a]	6/21	29%	2/20	10%	3.60	0.6–20.5	0.24
Recanalisation rate (full or partial) ($n=41$)[a]	18/21	86%	15/20[b]	75%	2.00	0.4–9.8	0.45
Time to recanalisation (days) ($n=41$)[a]	45	23–118	30	22–72	NA	NA	0.50

Note: The data are expressed as *n/N* (%) or the median [interquartile range].

Abbreviations: ACT, anti-coagulation therapy; CI, confidence interval; IQR, interquartile range; NA, not applicable; OR, odds ratio; PICU, paediatric intensive care unit.

[a]Number of survivors.

[b]Five of the 20 patients without follow-up imaging.

thrombosis sites (Table 3). The median CRP was significantly lower in patients with no neurological signs and symptoms on admission. Only one of the patients with no neurological signs and symptoms on admission had sequelae. Eight days after admission, he presented signs of intracranial hypertension, impaired consciousness, and hemiparesis, due to a worsening of his empyema and ischemic lesions. Only one patient with neurological signs and symptoms at diagnosis was not hospitalised in the PICU. He presented with sigmoid sinus thrombosis (due to acute mastoiditis) and binocular diplopia (due to abducens nerve paralysis). The diplopia resolved after a few days, and there were no sequelae.

In the subgroup of patients with mastoiditis ($n=23$), 14 (61%) did not receive ACT (Table 4); most of the patients in this subgroup had thrombosis of the sigmoid sinus ($n=20$), internal jugular vein ($n=13$) or transverse sinus ($n=10$). In four patients, the thrombosis had spread to other sinuses. Children with versus without mastoiditis did not differ significantly with regard to the extent of CVT and the number of sinuses involved. When compared with patients with non-otogenic CVT, patients with mastoiditis were less likely to be admitted to the PICU ($p=0.02$), to receive ACT ($p=0.04$) and to present with neurological signs and symptoms on admission ($p=0.01$). Patients with mastoiditis were less likely to present

TABLE 3 Comparison of patients with versus without neurological signs and symptoms on admission.

	Neurological signs or symptoms on admission						
	Yes ($n=17$)		No ($n=26$)				
Variables	*n/N* or median	% or IQR	*n/N* or median	% or IQR	OR	95% CI	*p*
Age (years)	5	0.75–13	4	2.25–7	NA	NA	0.61
Male sex	13/17	76%	14/26	54%	2.79	0.7–10.9	0.13
Family history of venous thrombosis	1/17	6%	1/26	4%	1.56	0.09–26.8	1
Immunodeficiency or immunosuppressive treatment	4/17	24%	2/26	8%	3.7	0.6–22.9	0.19
Initial ENT infection							
Mastoiditis	4/17	24%	19/26	73%	0.11	0.03–0.5	<0.01
Sinusitis	6/17	35%	4/26	15%	3	0.7–12.9	0.16
Meningitis	7/17	41%	0/26	0%	37.9	2–723.8	<0.01
Pharyngeal abscess	0/17	0%	3/26	12%	0.2	0.01–4	0.27
Admission to the PICU	16/17	94%	13/26	50%	16	1.8–139	<0.01
Anti-coagulation therapy	13/17	76%	10/26	38%	5.2	1.3–20.5	<0.01
Empyema	8/17	47%	11/26	42%	1.2	0.4–4.1	0.76
Vasculitis	4/17	24%	0/26	0%	17.7	0.9–352.8	<0.01
C-reactive protein (mg/L) ($n=39$)	254	219–307	211	141–232	NA	NA	<0.01
White blood cell count (G/L) ($n=30$)	19	6.75–27	17	13.5–22.2	NA	NA	0.86
Thrombosis site							
Sigmoid sinus	6/17	35%	20/26	77%	0.2	0.04–0.6	<0.01
Internal jugular vein	4/17	24%	16/26	62%	0.2	0.05–0.8	<0.01
Transverse sinus	7/17	41%	10/26	38%	1.1	0.3–3.9	0.86
Other	12/17	71%	6/26	23%	8	2–32	<0.01
Bilateral thrombosis	2/17	12%	1/26	4%	3.3	0.3–40	0.55
Number of thrombosis site	1	1–2	2	1–3	NA	NA	0.26
Multiple thrombosis	7/17	41%	12/26	46%	0.8	0.2–2.8	1
Venous occlusion imaging score	1	1–2	2	1–3	NA	NA	0.38
Neurological sequelae ($n=41$)[a]	7/15	47%	1/26	4%	21.9	2.3–205.8	<0.01
Recanalisation rate (full or partial) ($n=41$)[a]	15/15	100%	18/26[b]	69%	0.07	0.004–1.3	0.07
Time to recanalisation (days) ($n=41$)[a]	45	22–232	38	20–94	NA	NA	0.49

Note: The data are expressed as *n/N* (%) or the median [interquartile range].

Abbreviations: CI, confidence interval; IQR, interquartile range; NA, not applicable; OR, odds ratio; PICU, paediatric intensive care unit.

[a]Number of survivors.

[b]Five of the 26 patients without follow-up imaging.

TABLE 4 Comparison of patients with mastoiditis-related CVT and patients with other infections.

	Mastoiditis						
	Yes ($n=23$)		No ($n=20$)				
Variables	*n/N* or median	% or IQR	*n/N* or median	% or IQR	OR	95% CI	*p*
Age (years)	4	1–9	5.5	2–11.25	NA	NA	0.60
Male sex	11/23	48%	16/20	80%	0.23	0.06–0.9	0.03
Family history of venous thrombosis	0/23	0%	2/20	10%	0.15	0.01–3.5	0.20
Immunodeficiency or immunosuppressive treatment	1/23	4%	4/20	20%	0.18	0.02–1.8	0.16
Neurological signs or symptoms on admission	4/23	17%	13/20	65%	0.11	0.03–0.5	<0.01
Admission to the PICU	12/23	52%	17/20	85%	0.19	0.04–0.8	0.02
Anti-coagulation therapy	9/23	39%	14/20	70%	0.28	0.08–0.98	0.04
Empyema	11/23	48%	8/20	40%	1.38	0.4–4.6	0.61
Vasculitis	0/23	0%	4/20	20%	0.08	0.04–1.5	0.04
C-reactive protein (mg/L) ($n=39$)	211	155–230	245	206–333	NA	NA	0.07
White blood cell count (G/L) ($n=30$)	18	12–22.9	18	7.75–26.2	NA	NA	0.81
Thrombosis site							
Sigmoid sinus	20/23	87%	6/20	30%	15.6	3.3–73	<0.01
Internal jugular vein	13/23	57%	7/20	35%	2.4	0.7–8.3	0.16
Transverse sinus	10/23	44%	7/20	35%	1.4	0.4–4.9	0.57
Other	4/23	17%	14/20	70%	0.09	0.02–0.4	<0.01
Bilateral thrombosis	1/23	4.3%	2/20	10%	0.41	0.03–4.9	0.59
Number of thrombosis site	2	1–3	2	1–2.25	NA	NA	0.93
Multiple thrombosis	14/23	61%	9/20	45%	1.9	0.56–6.4	0.3
Venous occlusion imaging score	2	1–3	2	1–2.25	NA	NA	0.93
Neurological sequelae ($n=41$)[a]	1/23	4%	7/18	39%	0.07	0.01–0.66	0.01
Recanalisation rate (full or partial) ($n=41$)[a]	18/23[b]	78%	15/18[c]	83%	0.72	0.15–3.5	1
Time to recanalisation (days) ($n=41$)[a]	30	22–99	51	23–114	NA	NA	0.63

Note: The data are expressed as *n/N* (%) or the median [interquartile range].

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; PICU, paediatric intensive care unit.

[a]Number of survivors.

[b]Two of the 23 patients without follow-up imaging.

[c]Three of the 18 patients without follow-up imaging.

sequelae ($p=0.01$) after 1 month of follow-up. The non-otogenic CVT group and the mastoiditis group did not differ significantly with regard to the full and partial recanalisation rates.

In the sub-group of patients with mastoiditis-related CVT and the subgroup of patients with no neurological signs or symptoms on admission, we compared the children having received ACT and those not having received ACT; there were no significant differences in the partial and total recanalisation rates or the other outcomes (Tables S3 and S4).

4 | DISCUSSION

In our cohort as a whole, 53% of patients with ENT-related CVT received ACT. Children were more likely to receive ACT if their condition was severe and they had been admitted to the PICU, which makes it difficult to draw any firm conclusions. Partial or total recanalisation was observed in 80% of the study population and did not depend on whether or not the child had received ACT. In patients with mastoiditis-related CVT and those with no neurological signs and symptoms on admission, ACT did not appear to influence the clinical and radiological outcomes. One of the 23 patients having received ACT experienced a severe side effect of ACT, with intracerebral hematoma and intracranial hypertension.

Although CVT has been studied extensively and its treatments are well known, there is no consensus on the management of cases related to an ENT infection. Septic CVT in paediatric populations has been studied even less frequently. However, an infection is the most common risk factor for CVT.[3,21] Infection-related CVT is probably under-diagnosed. In a 4-year study of ACT in 500 patients at

107 centres worldwide, 114 presented with CVT, and only 74 of those had a concomitant ENT infection.[22] The apparent incidence of infection-related CVT might have been lowered by the systematic use of antibiotics to treat suppurative complications of ENT infections and by failure to perform appropriate imaging.[23,24]

In similar studies of 52 and 16 patients, respectively, Coudert et al. and Coutinho et al. did not identify any haemorrhagic complications of ACT.[6,25] Haemorrhagic complications are rare but do occur. One of the patients had severe temporal haematoma. In a review of the literature data on mastoiditis in children, ACT-associated bleeding was described in eight (7%) of the 113 patients.[10] The risk of haemorrhage is higher after surgery, which is frequently required in patients with severe infections. In order to limit the risk of intracranial bleeding associated with ACT, it makes sense to look for cases of CVT resulting from ENT infections in which ACT has no benefit.

In the present study, these clinical situations corresponded to patients with otogenic thrombosis and those not presenting neurological signs and symptoms on admission. These patients did not gain any benefit from ACT in terms of the recanalisation rates, the time to recanalisation, and the outcomes. Other researchers have suggested that ACT is of no benefit in these specific patients, with a shorter time to recanalisation, occasional spontaneous recanalisation in the absence of ACT, and no sequelae at last follow-up.[6,10–12,25–27] A study of 84 patients showed that although ACT was administered significantly less frequently in an infection-related CVT group, the time to complete recanalisation was nevertheless shorter.[26] In the review by Wong et al., 113 (59%) of the 190 of patients with mastoiditis-related CVT received ACT.[10] Of the 117 patients with a documented follow-up CT scan; 59 (51%) had full recanalisation, 35 (30%) had partial recanalisation, and 17 (15%) had persistent occlusion.

4.1 | Strengths and limitations

Our study had a number of strengths. Firstly, the number of patients with infection-related CVT was greater than in other studies of this topic; our cohort of children with infection-related CVT is one of the largest to date. Secondly, and although the cohort was heterogeneous as in other similar studies, it was representative of the patient population: male predominance, a median age of 4 years, a majority of cases of transverse or sigmoid sinuses thrombosis, and a high proportion of cases of mastoiditis.[8,11,26] *Streptococcus intermedius* was the most frequently detected bacterium, although 19% of the patients with documented pathogens presented with a *Fusobacterium necrophorum* infection.[8,11,26] Thirdly, all the data for the primary objective were reviewed by an independent neuroradiologist, who was blinded to the clinical outcome and treatment. Lastly, the validated venous occlusion image score was used to score the extent of the thrombosis in a standardised way.

Our study also had limitations. Firstly, the number of study participants was relatively small; this reduced the statistical power, particularly in subgroup analyses. A multicentre study would increase statistical power and enable multivariable analyses but would be limited by differences in practice from one centre to another. Secondly, the study's retrospective design posed methodological issues with regard to systematic brain imaging during follow-up. Lastly, the time interval between treatment of the CVT and the first follow-up imaging was not standardised and varied greatly. Despite this limitation, data on re-canalisation were available for 88% of the included patients; this proportion is similar to or higher than those reported in other studies.[3,10]

In our study, as in others, ACT was not administered in all cases of CVT; only half of the patients received the therapy. In a literature review of 67 publications, ACT was administered to 51 (64%) of 80 patients with ENT-infection-related CVT. In a more recent review of 22 study cohorts ($n = 312$ children) with otogenic CVT, ACT was administered in 86% [95% CI, 75–95] of cases.[28] This might be due to the current guidelines, which recommend the systematic use of ACT in CVT in the absence of associated intracranial haemorrhage.[29,30] The 2021 French national guidelines published at the end of this study period recommended systematic ACT in cases of CVT, regardless of the infectious status, the thrombosis site and clinical presentation. The only change was the duration of administration.[29] The investigation of hypercoagulable status is recommended in cases of CVT with a low risk of thrombosis, such as local infection.

Our present findings go against the French national guidelines and suggest that the unnecessary administration of ACT can be reduced, which would help to avoid bleeding complications. However, this strategy must be modulated by the clinical outcomes in the first few days and the radiological follow-up, with a screen for extension of the thrombosis to other sites or worsening of the symptoms. Further studies are needed to identify patients who will present spontaneous recanalisation of post-infectious CVT after the administration of appropriate surgical and anti-microbial treatments only.

5 | CONCLUSION

This study was designed before the publication of the 2021 French guidelines recommending ACT for all patients with infectious CVT. The results enabled us to determine the absence of value of ACT in certain circumstances. Half of the included patients were treated with ACT. Partial or total recanalisation was observed in 80% of the patients, including some who had not received ACT. ACT did not appear to influence the clinical and radiological outcomes in patients with mastoiditis-related CVT and in patients with no neurological signs or symptoms on admission.

AUTHOR CONTRIBUTIONS

Juliette Eloy: Conceptualization; investigation; writing – original draft; methodology; validation; writing – review and editing; data curation; formal analysis. **Audrey Hochart:** Conceptualization; writing – original draft; methodology; writing – review and editing; visualization.

Gustavo Soto-Ares: Investigation; formal analysis; supervision; visualization; writing – review and editing; validation. **Marion Lagree:** Visualization; writing – review and editing; conceptualization; validation. **Grégory Kuchcinski:** Validation; formal analysis; visualization; writing – review and editing. **Mélodie-Anne Karnoub:** Validation; visualization; writing – review and editing. **Alix Maltezeanu:** Validation; visualization; writing – review and editing. **Stéphane Leteurtre:** Validation; visualization; writing – review and editing; supervision. **François Dubos:** Conceptualization; methodology; validation; supervision; visualization; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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