MRI of acute osteomyelitis in long bones of children: Pathophysiology study

C. Thévenin-Lemoine[a,*], J. Vial[b], J.L. Labbé[c], B. Lepage[d], B. Ilharreborde[e], F. Accadbled[a], la SOFOP

[a] *Service d'orthopédie pédiatrique, hôpital des Enfants, Toulouse, France*
[b] *Service d'imagerie médicale pédiatrique, hôpital des Enfants, Toulouse, France*
[c] *Service de chirurgie orthopédique, centre hospitalier térritorial de Nouvelle Calédonie, Nouméa, New Caledonia*
[d] *Service d'épidémiologie médicale, hôpital Purpan, Toulouse, France*
[e] *Service d'orthopédie pédiatrique, hôpital Robert-Debré, Paris, France*

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A B S T R A C T

Introduction: The classic pathophysiology of acute osteomyelitis in children described by Trueta has a metaphyseal infection as the starting point. This hypothesis was recently brought into question by Labbé's study, which suggested a periosteal origin. Thus, we wanted to study this disease's pathophysiology through early MRI examinations and to look for prognostic factors based on abnormal findings.
Material and methods: This was a prospective, multicentre study that included cases of long bone osteomyelitis in children who underwent an MRI examination within 7 days of the start of symptoms and within 24 hours of the initiation of antibiotic therapy. We also collected clinical, laboratory and treatment-related data.
Results: Twenty patients were included, including one with a bifocal condition. The lower limb was involved in most cases (19/21). *Staphylococcus aureus* was found most frequently. Metaphyseal involvement was present in all cases. No isolated periosteal involvement was found in any of the cases. No prognostic factors were identified based on the various abnormal findings on MRI.
Conclusion: Our study supports the metaphyseal origin of acute osteomyelitis in children.
Level of evidence: II.

1. Introduction

Acute osteomyelitis (AOM) is a bone infection that spreads hematogenously. The incidence is 1 case per 5000 to 10,000 people per year in France, with the lower limb involved in 70% of cases [1]. Imaging has a predominant role in the diagnosis of AOM. Although bone scan imaging has long been the gold standard, it has been replaced by magnetic resonance imaging (MRI) because of the possibility of detailed analysis of tissue involvement and its non-irradiating character. It has excellent sensitivity (98%) and specificity (92%) [2].

The pathophysiology of acute osteomyelitis in children, as described by Trueta [3] more than 60 years ago has metaphyseal inoculation as the primary cause, from which an intra-osseous abscess forms that can spread to form a subperiosteal abscess. This pathophysiological mechanism was recently questioned by Labbé et al. [4]; their ultrasonography study suggested that the primary cause was actually periosteal inoculation. This hypothesis was recently fuelled by the publication of a case report [5]. But to our knowledge, no study up to now has investigated AOM pathophysiology using modern means.

Hence, we carried out a study in which the primary objective was to evaluate whether performing MRI early on would help to clarify the pathophysiology of AOM. The secondary objective was to bring to light, based on the abnormal MRI findings, any relationships with age, bone location, causative bacterium, initial laboratory findings, progression with treatment and occurrence of complications.

2. Material and methods

This was a prospective, observational, multicenter, non-randomised study under the auspices of the French Paediatric Orthopaedic Society (SOFOP). Six sites participated in the

Table 1
Results.

Patient	Gender	Age (years)	Duration symptoms (d)	Bone	CRP (ng/mL)	Blood culture	Bone biopsy	Secondary surgery	Clinical regression (day 3)	CRP day 3 (ng/mL)	Clinical regression (day 45)	CRP day 45 (ng/mL)	X-rays day 45
1	M	8.5	3	Distal femur	155.8	MSSA		No	Yes	32	Yes	5	Periosteal apposition
2	F	3	1	Distal femur	88	MSSA		No	Yes	68.3			Normal
3	F	11.5	5	Proximal tibia	157.9	MSSA		Abscess	No	248	Yes	1.02	Lysis and periosteal apposition
4	F	9	3	Proximal tibia	63.7	Negative		No	Yes	20.9	Yes	2	Normal
5	M	6.1	1	Distal tibia	187	MRSA		Abscess	Yes	53	Yes	10	Normal
6	M	1.4		Proximal radius	36	Negative		No	Yes	10			
7	M	6.6	3	Distal femur	221	MSSA		Abscess	No	103	Yes	10	Periosteal apposition
8	F	1.1	3	Proximal femur	9	Negative		No	Yes		Yes	10	Normal
9	M	12	6	Proximal femur	97	MSSA	MSSA	Abscess	No	137.8	Yes	1	Normal
10	M	13	1	Proximal tibia	26.1	MSSA	MSSA	Abscess	Yes	24.8	Yes	1	Normal
11	M	9	2	Distal tibia	78	Negative		No	No	180	Yes	1	Periosteal apposition
12	M	12	2	Proximal femur	90	MSSA		No	No	125	Yes	1.4	Periosteal apposition
13	M	7	1	Proximal tibia	140	CoNS	MSSA	Abscess	Yes	45.5	Yes	3.2	Lysis and periosteal apposition
14	F	7	4	Distal tibia	151	Negative		No	No	176	Yes	13	Periosteal apposition
15	M	4.5	1	Distal fibula	37	Negative	MSSA	No	Yes	24	Yes	2	Normal
16	M	13.3	1	Distal femur and proximal tibia	76	MSSA	MSSA	No	No		Yes	5	Lysis
17	M	6	4	Distal tibia	18		MSSA	No	Yes	24	Yes	5	Lysis
18	M	2.5	1	Distal ulna	16	Negative	MSSA	No	Yes	2	Yes	2	Lysis
19	M	5.3	5	Proximal tibia	45	MSSA	MSSA	No	Yes	11	Yes	10	Normal
20	F	3.3	3	Proximal fibula	151	Negative	*S. pyogenes*	No	Yes	103	Yes	6	Lysis
Mean		7	2.6		92					77		5	

MSSA: Methicillin-susceptible *Staphylococcus aureus*; MRSA: Methicillin-resistant *Staphylococcus aureus*; CoNS: Coagulase-negative *Staphylococcus*, *S. pyogenes*: *Streptococcus pyogenes*.

Table 2
Abnormal findings on MRI.

Patient	Bone	Time to MRI (days)	Metaphysis	Diaphysis (mm)	Physis (mm)	Epiphysis (mm)	SP abscess (mm)	ST extension	ST abscess	Metaphyseal abscess	Joint involvement	Devascularization (mm)
1	Distal femur	4	Yes	No	30	36	40	Yes	No	No	Yes	34
2	Distal femur	3	Yes	No	14	No	38	Yes	No	No	Yes	22
3	Proximal tibia	6	Yes	100	20	53	24	Yes	No	No	No	10
4	Proximal tibia	4	Yes	No	14	25	No	Yes	No	No	No	12
5	Distal tibia	2	Yes	No	9,5	No	97	Yes	No	No	Yes	14
6	Proximal radius	7	Yes	67	No	No	21	Yes	No	No	No	No
7	Distal femur	2	Yes	80	40	13	80	Yes	10	10	Yes	63
8	Proximal femur	7	Yes	No	No	No	No	Yes	No	No	No	No
9	Proximal femur	6	Yes	140	No	No	22	Yes	No	No	No	66
10	Proximal tibia	2	Yes	No	No	No	No	Yes	No	No	No	No
11	Distal tibia	5	Yes	No	No	No	No	No	No	No	No	No
12	Proximal femur	4	Yes	No	No	No	No	Yes	No	No	No	No
13	Proximal tibia	2	Yes	No	12	No	40	Yes	No	No	Yes	No
14	Distal tibia	5	Yes	No	9	6	No	Yes	No	No	No	No
15	Distal fibula	3	Yes	No	11	12	25	Yes	No	No	Yes	9
16	Distal femur and proximal tibia	2	Yes	No	8 11	12 18	No	Yes	No	No	Yes	5 17
17	Distal tibia	5	Yes	75	7.5	17	No	Yes	No	No	Yes	20
18	Distal ulna	2	Yes	80	No	No	No	Yes	21	Yes	Yes	14
19	Proximal tibia	5	Yes	No	6.5	10	No	Yes	No	No	No	9.5
20	Proximal fibula	3	Yes	No	No	No	No	Yes	No	No	No	6
Mean		4		90	15	20	43		16	10		22

SP: subperiosteal; ST: soft tissues.

study (Fort-de-France, Genève, Lille, Nouméa, Robert-Debré and Toulouse). The study was approved beforehand by the French Advisory Committee for Data Processing in Health Research (CCTIRS).

Over the 1-year inclusion period, any child between 1 and 15 years of age with AOM of the long bones, diagnosed by increased uptake on bone scan or by bone or periosteal inflammatory signals on MRI, in the absence of trauma or signs of tumour proliferation, was included. Microbiological confirmation was not mandatory. An MRI was performed at the latest 7 days after the appearance of clinical signs using a standardised protocol established by the French Paediatric and Prenatal Imaging Society (SFIPP): T1 and STIR (short tau inversion recovery) sequences in the long axis of the limb; axial T2 sequence and biplanar T1 sequences with fat-saturation (Fat-Sat) and intravenous injection of gadolinium chelate, one of which was in the long axis of the limb. Sub-acute and chronic (defined by presence of radiographic changes) osteomyelitis cases were excluded, as were those in whom the antibiotic therapy had been started more than 24 hours before the MRI. The MRI checklist captured the following data: location of the infection (which bone, epiphysis-metaphysis-diaphysis location, proximal or distal), extent of diaphyseal involvement, extension to growth plate or epiphysis, presence of subperiosteal abscess, soft tissue extension, joint involvement and devacularized area. For the quantitative parameters, the largest dimension was measured in millimetres. A devascularized area was defined as the presence of a hypointense signal in an intra-osseous area in all the sequences that did not have increased gadolinium uptake. It was differentiated from an intra-osseous abscess by the absence of a fluid centre and peripheral gadolinium uptake. All the MRI sequences were read by a senior radiologist (JV). The following data were also collected at enrolment: age, presence of fever, local inflammatory signs and laboratory findings (CBC, SR, CRP and blood cultures). At day 3 ($\pm$ 1 day) of the hospital stay, clinical signs, CRP levels and data related to the antibiotics (molecule, dosage and start date) were collected. At the day 45 follow-up visit ($\pm$ 5 days), clinical signs, CRP levels, radiographic findings (normal, osteolysis, periosteal new bone formation) and the end date of antibiotics were recorded.

Clinical and imaging data were collected for all the children and lesions. The need for secondary surgery, clinical regression and CRP levels on day 3, along with the presence of abnormal radiological findings, and the CRP levels on day 45 were compared based on features found on MRI (Fisher's exact test). An alpha of 5% was used with each test. This analysis was performed using Stata SE 11.2 software.

3. Results

The study included 14 boys and 6 girls, with an average age of 7.1 years (1.1–13.3) (Tables 1 and 2). The average duration of symptoms at the time of the MRI was 4 days (2–7). The infection was located in the tibia in 10 cases, femur in 7 cases, fibula in 2 cases, radius in 1 case and ulna in 1 case. One patient had two foci of infection (femur and tibia). At the time of the diagnosis, the average body temperature was 38.7 °C ($\pm$ 1), the average CRP was 92 ng/mL (9–221) and the average white blood cell count was 11,400/mm^3 (4600–31,920). Blood cultures were positive in 10 cases (50%), all for *Staphylococcus aureus*; three cultures secreted toxins (panton–valentine leukocidin [PVL] in two cases and toxic shock syndrome toxin-1 [TSST-1] in one case). One positive *S. epidermidis* sample was considered cross contaminated. A bone biopsy was performed in nine cases (45%), with 100% positive rate. Cross-referencing of blood cultures with local sampling led to bacterial identification in 15 cases (75%): 14 *S. aureus* and 1 *Streptococcus pyogenes*.

Ultrasonography was performed in eight cases, with three showing evidence of a subperiosteal abscess. Bone scan was performed in four cases, all of which showed increased uptake. MRI revealed metaphyseal involved in all cases, characterised by an inflammatory signal with increased uptake after injection (Figs. 1 and 2). The diaphysis was involved in 6 cases (29%), metaphysis in 13 cases (62%) and epiphysis in 10 cases (48%) (Fig. 3). A devascularized area (Fig. 4) was identified in 14 cases (67%) and joint involvement in 10 cases (48%). A subperiosteal abscess (Fig. 5) was found in nine cases (43%) and a metaphyseal abscess (Fig. 6) in two cases (10%). Soft tissue extension was found in 20 cases (95%) with an abscess (Fig. 5b) in two cases (10%).

Surgery to drain the subperiosteal abscess was done in six cases (29%). The initial course of antibiotics was given through the peripheral intravenous route. Monotherapy was used in 12 cases and bitherapy in 8 cases. The main antibiotic was penicillin in 11 cases, cephalosporin in 8 cases and vancomycin in 1 case. The second antibiotic was gentamicin in seven cases and clindamycin in

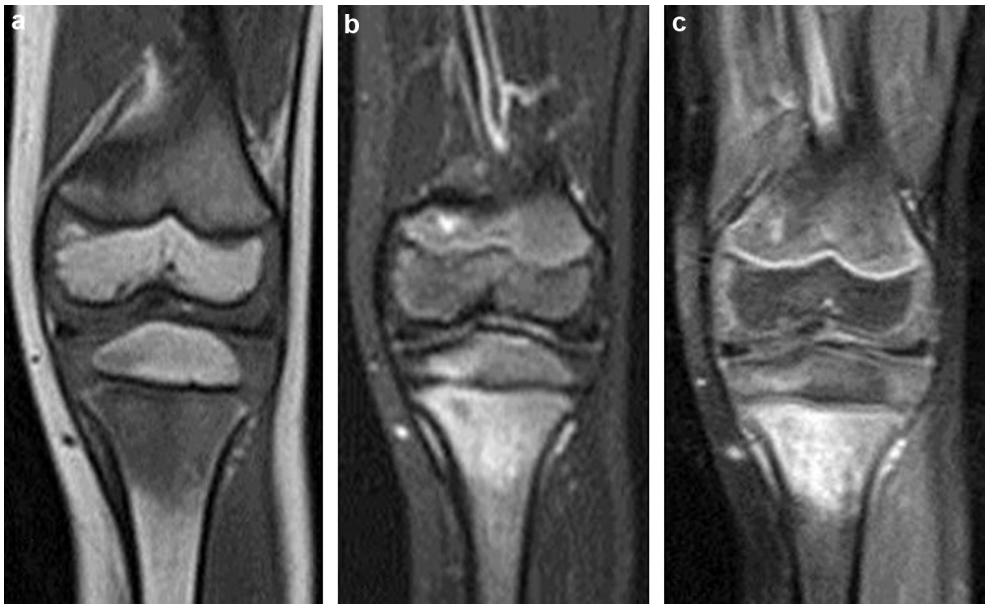

Fig. 1. Acute osteomyelitis of the proximal tibia with an area of intramedullary oedema in the metaphysis with T1 hypointensity (a), STIR hyperintensity (b) and increased gadolinium uptake (c).

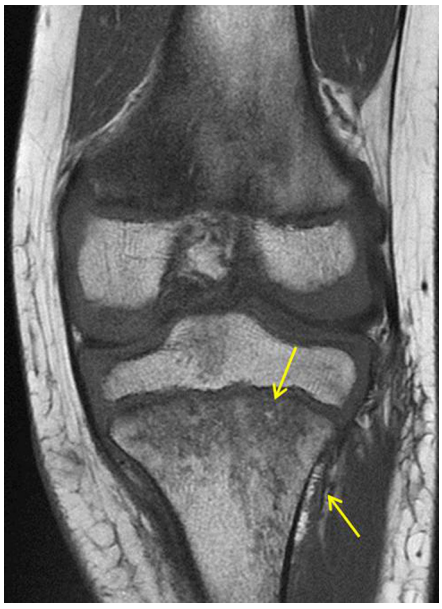

Fig. 2. Punctiform hyperintensity on T1 sequences in the medullary canal and subperiosteal space suggestive of acute osteomyelitis of the proximal tibia.

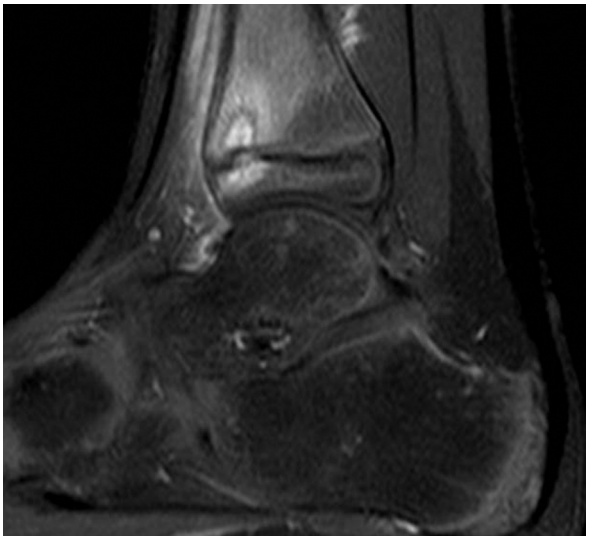

Fig. 3. Lesion with STIR hyperintensity in the metaphysis and epiphysis junction of the distal tibia with hypointense sclerotic margins and hyperintense peripheral oedema.

one case. The average duration of intravenous antibiotic therapy was 7.4 days (2–18). The average duration of the oral continuation therapy was 34.9 days (14–75). The oral antibiotics were mainly clindamycin (9 cases) or amoxicillin–clavulanic acid (6 cases). At day 45, all of the abnormal clinical and laboratory findings were completely normal in every case. Radiological analysis at day 45 found periosteal new bone formation in five cases, osteolysis in four cases and both in two cases.

We found no link between the duration of symptoms and the various abnormal MRI findings described. There was a statistically significant relationship between the presence of a subperiosteal abscess and surgery being performed (55.6% vs. 9.1%; $P = 0.05$). However, there was no relationship with any of the other abnormal MRI findings described. We found no statistical relationship between the various MRI criteria and the regression of clinical signs and CRP levels on days 3 and 45. We also found no statistical relationship between the various MRI criteria and abnormal radiological changes on day 45.

4. Discussion

The goal of this study was to test the hypothesis that osteomyelitis had a periosteal origin by performing MRI early on in the disease course. We could not confirm this hypothesis, as metaphyseal involvement was present in every case and no case had an isolated subperiosteal abscess. Looking back at the published studies suggesting a periosteal origin, the diagnosis in the Labbé study [4] was based on ultrasonography or computed tomography, which may have been unable to detect an underlying intra-osseous infection. In the case report by Weenders et al. [5], although there was predominant periosteal involvement, there also appears to be metaphyseal involvement in the published images.

The main limitation of our study is its lack of statistical power due to the small sample size. This can be explained by the restric-

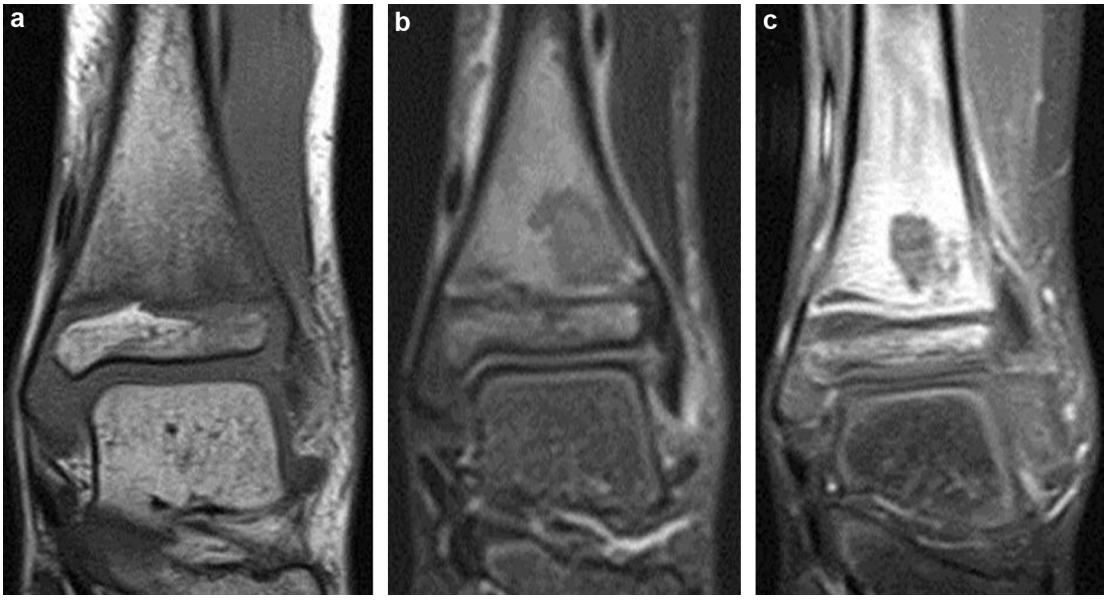

Fig. 4. Hypointense intra-osseous area on T1 (a), hypointense T2 Fat-Sat (b) without increased gadolinium uptake (c), suggestive of devascularized area in the distal tibia.

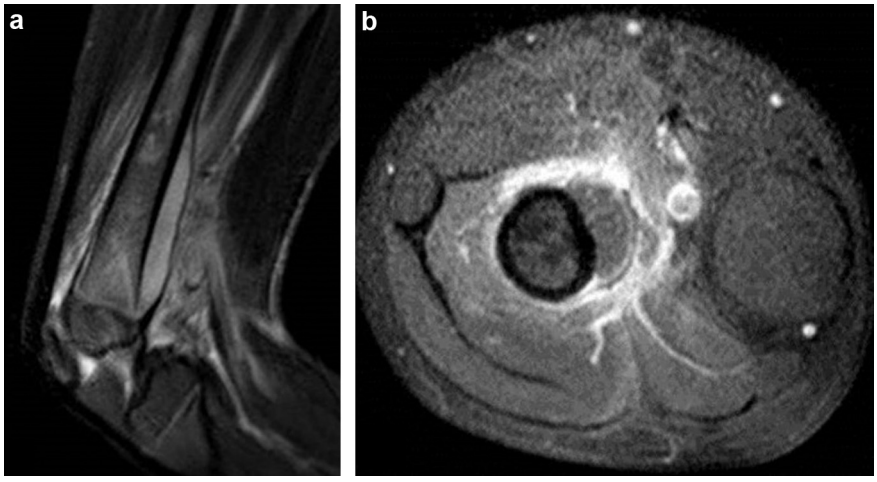

Fig. 5. Subperiosteal abscess of the distal femur with fluid centre based on STIR hyperintensity (a) with increased uptake in the peripheral shell (b), with small soft tissue abscess in contact with the periosteal one.

tive inclusion and exclusion criteria, particularly the requirement to carry out the MRI before or within 24 hours of the initiation of antibiotics. In fact, the availability of MRI is still limited [6] and we did not want it to delay the initiation of antibiotics for the purpose of this study.

If we compare our study to other published French studies [7,8] (comparable in terms of the bacterial ecology), it is interesting to note that our selection criteria induced a selection bias (Table 3). Performing an MRI is more complicated in smaller children, sometimes requiring general anaesthesia. As a consequence, the average age of our study population was relatively high (7.1 years). The selection of an older sub-population explains the predominance of *S. aureus*, high initial CRP levels (95 ng/mL) and high number of positive blood cultures (60%). This means that *Kingella kingae* infections were excluded as they are only present in children under 4 years of age [8]. The fact that we focussed solely on the long bones may also have contributed to excluding *Kingella* infections, as small bone involvement is characteristic of this bacteria [9].

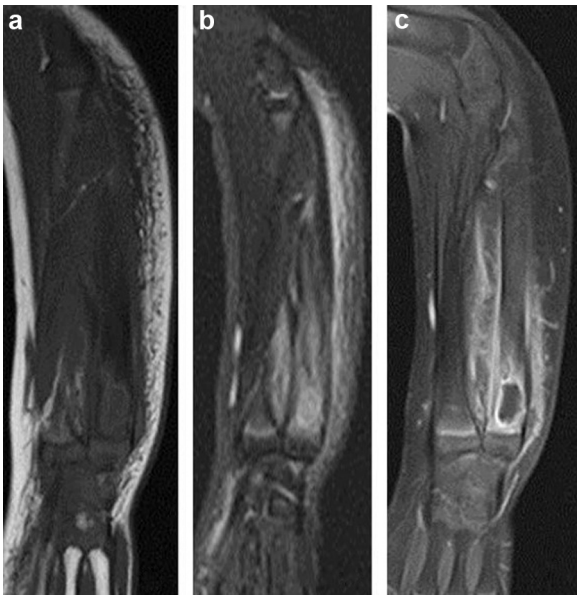

Fig. 6. Ulnar distal metaphyseal intra-osseous abscess in a 2-year-old child with oval liquid centre in T1 hypointensity (a), STIR hyperintensity, (b) without increase gadolinium uptake (c). The injected sequences help to clearly see the ring-shaped uptake in the wall of the abscess (c).

Table 3
Comparison of published French studies on acute osteomyelitis.

	Doit et al. [7]	Ferroni et al. [8]	Current study
Age (years)	2.3	3.4	7.1
CRP (ng/mL)		45	98
Blood culture (%)		9.7	60
Staphylococcus aureus (%)	67	57	93
Kingella kingae (%)	5	30	0

In our study, the total duration of antibiotic therapy was long: the mean duration of intravenous treatment was 7 days (2–18) and the oral treatment was 35 days (14–75). This is much longer than recent recommendations of 2–4 days of intravenous treatment and 21 days of total treatment [10,11]. In reality, because of the strong inflammatory syndrome, the treatment had to be extended until the clinical and laboratory signs had normalized.

We also could not identify prognostic factors for abnormal MRI findings. This could also have been due to the study's low statistical power, but also to the antibiotic therapy's good efficacy, with a 100% healing rate at day 45. There also was no correlation between MRI lesions and the duration of symptoms. This made it impossible to establish a chronology for the appearance of these lesions. We also found no link between abnormal MRI findings and the type of microorganism due of the predominance of *S. aureus* in our study.

MRI made it possible to diagnose more subperiosteal abscesses (9 cases) than ultrasonography (3 cases). This may have led to more surgical procedures being performed in our study than ultrasonography only (7 cases, 35%). This leads us to wonder whether certain abscesses could have resolved with antibiotics only and if there is a critical abscess size that should be drained surgically.

Thus, it seems essential to extend this type of study, since a larger population will be needed to define prognostic factors. It is also possible that one day we will better modulate the type and duration of the antibiotic therapy based on these factors, in a manner that optimises antibiotic usage.

5. Conclusion

Our study supports a metaphyseal origin for osteomyelitis but can not eliminate the possibility of forms with a periosteal origin. Various abnormal changes were found on MRI, but no prognostic value could be identified. The implication of these findings from a therapeutic viewpoint needs to be defined with a larger study population.

Disclosure of interest

The authors declare that they have no competing interest.

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