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Diagnostic, clinical management, and outcome of bone flap-related osteomyelitis after cranioplasty

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ABSTRACT

Objectives: We aimed to describe diagnostic, management, and outcome of bone flap-related osteomyelitis after cranioplasty.
Methods: Patients followed up in our tertiary care hospital for bone flap-related osteomyelitis after cranioplasty were included in a retrospective cohort (2008-2021). Determinants of treatment failure were assessed using logistic regression and Kaplan-Meier curves analysis.
Results: The 144 included patients (81 [56.3%] males; median age 53.4 [interquartile range [IQR], 42.6-62.5] years) mostly presented wound abnormalities (n = 115, 79.9%). All infections were documented, the main pathogens being *Staphylococcus aureus* (n = 64, 44.4%), *Cutibacterium acnes* (n = 57, 39.6%), gram-negative bacilli (n = 40, 27.8%) and/or non-*aureus* staphylococci (n = 34, 23.6%). Surgery was performed in 140 (97.2%) cases, for bone flap removal (n = 102, 72.9%) or debridement with flap retention (n = 31, 22.1%), along with 12.7 (IQR, 8.0-14.0) weeks of antimicrobial therapy. After a follow-up of 117.1 (IQR, 62.5-235.5) weeks, 37 (26.1%) failures were observed: 16 (43.2%) infection persistence, three (8.1%) relapses, 22 (59.5%) superinfections and/or two (1.7%) infection-related deaths. Excluding superinfections, determinants of the 19 (13.4%) specific failures were an index craniectomy for brain tumor (odds ratio = 4.038, $P = 0.033$) and curettage of bone edges (odds ratio = 0.342, $P = 0.048$).
Conclusion: Post-craniectomy bone flap osteomyelitis are difficult-to-treat infection, necessitating prolonged antimicrobial therapy with appropriate surgical debridement, and advocating for multidisciplinary management in dedicated reference centers.

Introduction

Cranioplasty is a common neurosurgical procedure, aiming to reconstruct a bone defect after skull opening. It can be carried out at the end of the surgery (craniotomy), or secondarily for example in the case of a two-stage decompression procedure (craniectomy), thus requiring temporary cryopreservation or subcutaneous storage

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in the abdomen of the autologous bone flap [1]. In addition to the metallic bone fixation devices, dura mater plasties are sometimes necessary, mostly using synthetic materials.

The global rate of surgical site infections after craniotomy/craniectomy has been estimated from 1-10% [2–5]. There is no specific epidemiological data according to the type of infection, ranging from skin and soft tissue infection to osteomyelitis, empyema, and brain abscess. These infections are associated with patient- and procedure-related risk factors, including diabetes, alcohol consumption, American Society of Anesthesiologists score, preoperative irradiation of the surgical area, non-compliance with either skin asepsis or antimicrobial prophylaxis guidelines, and prolonged surgery [3,6,7]. Turning specifically to bone flap infection, smoking, allergy, and fever on day 1 after surgery have been associated with higher rate of osteomyelitis [8].

Bone flap-related osteomyelitis after cranioplasty is uncommon but associated with high morbidity and healthcare expenditures [9]. The management of these difficult-to-treat infections relies on little data and no specific guidelines. As a result, the management is driven largely by experience with other bone, joint, or prosthetic joint-related infections. Removal of the infected bone flap is usually proposed along with prolonged antimicrobial therapy, before a delayed new cranioplasty, mostly using non-biological materials [10,11]. These strategies have poorly been evaluated. In this context, we assessed clinical and microbiological features, management, and outcome of bone flap-related osteomyelitis after cranioplasty in a retrospective cohort study.

Methods

Study design and included population

All adult (≥18 years) patients followed up in the infectious disease department of our tertiary care institution—hosting one of the French reference centers for the management of complex bone and joint infection (CRIOAc)—were included in a retrospective cohort study (2008-2021). Infections occurring on synthetic cranioplasty were excluded, as well as patient follow-up less than 3 months after last surgery. Diagnostic features (including clinical, microbiological, biological, and radiological data), surgical and medical management, and outcomes were collected from medical records in an anonymous case report form. Comorbidities were summarized according to the American Society of Anesthesiologists score and the modified Charlson Comorbidity Index. In the absence of guidelines or formalized protocol, surgical strategies (i.e., indications for bone flap and/or dura plasta removal) were left at the appreciation of the treating surgeon.

Definitions

In the absence of specific definitions of bone flap-related osteomyelitis after cranioplasty, infection, and diagnosis/management concepts were largely based on current guidelines for periprosthetic joint infection [12,13].

Bone flap-related osteomyelitis was considered in the presence of clinical (fever, sinus tract, or any other wound event), radiological (bone lysis, empyema, or contiguous brain abscess), microbiological and/or histological signs of osteomyelitis, and if managed as such by the treating physicians. Infections were classified according to timing from cranioplasty to first appearance of symptoms in early (<3 months), delayed (3-12 months), and late (>12 months) infection. Additionally, infections were classified as acute or chronic, with acute infections being surgically managed within 4 weeks or fewer.

Regarding microbiological diagnosis, deep surgical samples were collected under sterile conditions and inoculated on various enriched media for prolonged (14 days) aerobic and anaerobic cultures. Two or more culture-positive intra-operative samples were considered significant for low virulent pathogens and/or potential contaminants (i.e., non-*aureus* staphylococci, *Corynebacterium* spp., *Cutibacterium acnes*) and at least one or more virulent pathogens (i.e., *Staphylococcus aureus*, streptococci/enterococci, or gram-negative bacilli [GNB]).

Combination antimicrobial therapy was defined as when two or more drugs were active on all the pathogens isolated at the infected site.

The primary endpoint was the global rate of treatment failure, including infection persistence under appropriate treatment, relapse (recurrence after antimicrobial therapy interruption), superinfection, and/or infection-related death. An outcome analysis excluding superinfection was also performed to address the rate and determinants of “specific” treatment failures. Patients for whom a long-term suppressive antimicrobial therapy had been decided upon initial surgery and with favorable clinical outcomes were not considered failures.

Statistical analysis

Studied variables were described as percentages for dichotomous variables and as medians with interquartile range (IQR) for continuous variables. In the percentage calculation, the number of missing values was excluded from the denominator. Nonparametric tests were used to compare groups (Chi-square, Fisher exact, and Mann-Whitney U tests), as appropriate.

Determinants of treatment failure were assessed using: (i) stepwise binary logistic regression, expressed as odds ratios (ORs) with their 95% confidence intervals (CIs); and (ii) Kaplan-Meier curves for treatment failure-free survival, compared between groups using the log-rank (Mantel-Cox) test. A P-value <0.05 was considered significant. All analyses were performed using SPSS v19.0 (SPSS, Chicago, IL, USA) and GraphPad-Prism v5.03 (GraphPad, San Diego, CA, USA).

Results

Included population

A total of 144 patients were included; 81 (56.3%) were male, with a median age of 53.4 (IQR, 42.6-62.5) years. Characteristics of the included patients are presented in Table 1.

Indications of index surgery were tumor removal (n = 88, 61.1%), decompression or reconstruction for trauma (n = 27, 18.8%), and ischemic (n = 15, 10.4%) or hemorrhagic (n = 10, 6.9%) strokes. They mostly consisted of craniotomy (n = 117, 81.3%), mainly performed for tumor removal (n = 87, 74.4%), trauma (n = 13, 11.1%), and stroke (n = 13, 11.1%). Two-stage procedures (craniectomy with secondary reconstruction) concerned 27 (18.8%) patients, mostly for trauma (n = 14, 51.9%) or stroke (n = 12, 44.4%), with a median delay for cranioplasty of 15.1 (IQR, 11.9-22.0) weeks after skull opening. Duraplasty was needed in 110/130 (84.6%) patients.

Bone flap infection characteristics

Most patients had early surgical site infection (n = 78, 54.2%), mainly presenting as wound abnormalities (n = 115, 79.9%). Fever was observed in 34 (23.6%) cases, only. Imaging by computerized tomography (CT) scan or magnetic resonance imaging was practiced in 137 (85.1%) patients, highlighting cerebral abscess, empyema, and/or bone lysis in 44 (32.1%), 42 (30.7%) and 31 (22.6%) cases, respectively.

Microbiological documentation was obtained for all patients, mostly through gold-standard deep surgical samples (n = 134,

Table 1
Description of the 144 included patients with bone flap-related osteomyelitis after cranioplasty, and comparison of patients with or without treatment failure, considering or not superinfections.

STUDY VARIABLES	TOTAL POPULATION	OUTCOME (ALL FAILURES)					OUTCOME (EXCLUDING SUPERINFECTIONS)				
		Successes	Failures	*P*-value[a]	OR (95% CI)[b]	*P*-value[b]	Successes	Failures	*P*-value[a]	OR (95% CI)[b]	*P*-value[b]
N	144	105	37				122	19			
DEMOGRAPHICS											
Sex (male)	81 (56.3)	60 (57.1)	20 (54.1)	0.745	0.882 (0.415-1.874)	0.745	70 (57.4)	9 (47.4)	0.397	0.659 (0.250-1.737)	0.399
Median age (years)	53.4 (42.6-62.5)	52.4 (41.4-62.5)	54.2 (46.5-62.6)	0.476	1.085 (0.852-1.383)	0.509	53.1 (42.0-62.4)	52.5 (47.6-60.6)	0.653	1.082 (0.792-1.478)	0.621
COMORBIDITIES											
Obesity (body mass index>30 kg/m²)	16 (11.3)	12 (11.5)	4 (11.1)	1.000	0.958 (0.288-3.185)	0.945	12 (9.8)	4 (22.2)	0.552	2.619 (0.742-9.241)	0.134
Irradiation at the infected site	27 (18.8)	18 (17.1)	9 (24.3)	0.338	1.554 (0.628-3.846)	0.341	22 (18.0)	4 (21.1)	0.760	1.159 (0.352-3.820)	0.808
Modified Charlson Comorbidity Index	3 (1-5)	3 (1-5)	3 (1-5)	0.789	0.979 (0.840-1.140)	0.781	3 (1-5)	3 (1-3)	0.404	0.917 (0.747-1.125)	0.404
American Society of Anesthesiologists score	2 (2-2)	2 (1-2)	2 (2-3)	0.321	1.276 (0.786-2.061)	0.327	2(2-2)	2 (2-2.5)	0.645	1.159 (0.625-2.149)	0.639
INDEX SURGERY											
Indication											
Tumor	88 (61.1)	60 (57.1)	26 (70.3)	0.160	1.773 (0.793-3.961)	0.163	69 (56.6)	16 (84.2)	**0.025**	4.038 (1.119-14.578)	**0.033**
Traumatic brain injury	27 (18.8)	19 (18.1)	8 (21.6)	0.638	1.249 (0.494-3.155)	0.639	24 (19.7)	3 (15.8)	1.000	0.773 (0.208-2.870)	0.701
Ischemic stroke	15 (10.4)	13.0 (12.4)	2 (5.4)	0.354	0.404 (0.087-1.884)	0.249	15 (12.3)	0 (0)	0.221	NC	NC
Hemorrhage	10 (6.9)	9 (8.6)	1 (2.7)	0.454	0.296 (0.036-2.422)	0.257	10 (8.2)	0 (0)	0.358	NC	NC
Size of bone flap (cm²)	45.5 (22.3-81.0)	48 (23-85)	42.0 (23.0-77.5)	0.784	0.998 (0.988-1.008)	0.691	45.5 (21.5-82.8)	55.0 (30.5-79.5)	0.787	1.001 (0.989-1.013)	0.826
Duraplasty	110/130 (84.6)	81/94 (86.2)	28/35 (80.0)	0.389	0.642 (0.233-1.770)	0.392	93 /111(83.8)	15/17 (88.2)	1.000	1.436 (0.302-6.829)	0.649
INFECTION CHARACTERISTICS											
Time from cranioplasty to symptoms (weeks)	8.9 (3.3-42.9)	8.9 (3.4-42.1)	12.6 (2.7-90.6)	0.871	1.000 (0.999-1.001)	0.442	9.4 (3.4-43.9)	7.6 (3.0-35.4)	0.675	0.999 (0.997-1.001)	0.336
Early infection (<3 months)	78 (54.2)	57 (54.3)	19 (51.4)	0.758	0.889 (0.420-1.882)	0.758	65 (53.3)	11 (57.9)	0.681	1.227 (0.462-3.260)	0.682
Delayed infection (3-12 months)	32 (22.2)	24 (22.9)	8 (21.6)	0.877	0.931 (0.376-2.303)	0.877	28 (23.0)	4 (21.1)	1.000	0.905 (0.278-2.947)	0.868
Late infection (>12 months)	34 (23.6)	24 (22.9)	10 (27.0)	0.609	1.250 (0.531-2.944)	0.610	29(23.8)	4 (21.1)	1.000	0.827 (0.255-2.683)	0.751
Clinical characteristics											
Fever	34 (23.6)	23 (21.9)	10 (27.0)	0.526	1.320 (0.559-3.122)	0.527	27 (22.1)	6 (21.6)	0.355	1.641 (0.570-4.724)	0.359
Sinus tract	52 (36.1)	37 (35.2)	15 (40.5)	0.565	1.253 (0.581-2.703)	0.565	42 (34.4)	9 (47.4)	0.296	1.674 (0.632-4.434)	0.300
Any other wound event	83 (57.6)	64 (61.0)	17 (45.9)	0.113	0.545 (0.256-1.160)	0.115	73 (59.8)	7 (36.8)	0.056	0.386 (0.142-1.050)	0.062
Neurologic deficiency	13 (9.0)	6 (5.7)	7 (18.9)	**0.017**	3.850 (1.202-12.336)	**0.023**	10 (8.2)	3 (15.8)	0.383	2.119 (0.526-8.527)	0.291
Cognitive impairment	35 (24.3)	27 (25.7)	7 (18.9)	0.405	0.674 (0.265-1.712)	0.407	31 (25.4)	3 (15.8)	0.564	0.556 (0.152-2.039)	0.376
Maximum C-reactive protein level (mg/l)	25.0 (7.0-87.0)	26.0 (8.5-80.0)	18.5 (3.0-93.8)	0.530	1.001 (0.995-1.008)	0.732	26.0 (9.0-84.0)	7 (2-87)	0.168	0.998 (0.989-1.007)	0.278
Imaging	137 (85.1)	101 (96.2)	35 (94.6)	0.651			118 (96.7)	17 (89.5)	0.183		
Bone lysis	31 (22.6)	23/101 (22.8)	8/35 (22.9)	0.992	1.005 (0.402-2.511)	0.992	24 (20.3)	6/17 (35.3)	0.189	2.051 (0.691-6.088)	0.196
Cerebral abscess	44 (32.1)	27/101 (26.7)	17/35 (48.6)	**0.017**	2.588 (1.168-5.738)	**0.019**	37 (31.4)	7/17 (41.2)	0.406	1.551 (0.548-4.393)	0.408
Empyema	42 (30.7)	29/101 (28.7)	13/35 (37.1)	0.352	1.467 (0.653-3.298)	0.354	36 (30.5)	6/17 (35.3)	0.674	1.258 (0.432-3.662)	0.674
Microbiological documentation											
S. aureus	64 (44.4)	48 (45.7)	15 (40.5)	0.586	0.810 (0.379-1.732)	0.786	55 (45.1)	8 (42.1)	0.831	0.899 (0.338-2.390)	0.831
Non-*aureus* staphylococci	34 (23.6)	25 (23.8)	8 (21.6)	0.786	0.883 (0.358-2.176)	0.787	29 (23.8)	4 (21.1)	1.000	0.864 (0.266-2.810)	0.809
Streptococcus spp.	15 (10.4)	13 (12.4)	2 (5.4)	0.354	0.404 (0.087-1.884)	0.249	14 (11.5)	0 (0)	0.221	NC	NC
Enterococcus spp.	6 (4.2)	3 (2.9)	3 (8.1)	0.182	3.000 (0578-15.569)	0.191	5 (4.1)	1 (5.3)	0.585	1.311 (0.145-11.875)	0.810

(*continued on next page*)

Table 1 (*continued*)

STUDY VARIABLES	TOTAL POPULATION	OUTCOME (ALL FAILURES)					OUTCOME (EXCLUDING SUPERINFECTIONS)				
		Successes	Failures	*P*-value[a]	OR (95% CI)[b]	*P*-value[b]	Successes	Failures	*P*-value[a]	OR (95% CI)[b]	*P*-value[b]
N	144	105	37				122	19			
Enterobacterales	28 (19.4)	20 (19.0)	8 (21.6)	0.735	1.172 (0.466-2.948)	0.735	24 (19.7)	3 (15.8)	0.766	0.735 (0.199-2.721)	0.645
Pseudomonas spp.	13 (9.0)	9 (8.6)	4 (10.8)	0.742	1.293 (0.373-4.479)	0.685	9 (7.4)	4 (21.1)	**0.075**	3.378 (0.925-12.332)	**0.065**
Cutibacterium acnes	57 (39.6)	44 (41.9)	13 (35.1)	0.470	0.751 (0.345-1.635)	0.471	49 (40.2)	8 (42.1)	0.851	1.098 (0.412-2.925)	0.851
Corynebacterium spp.	5 (3.5)	3 (2.9)	2 (5.4)	0.605	1.943 (0.312-12.111)	0.477	3 (2.5)	2 (10.5)	0.133	4.706 (0.733-30.226)	0.103
Polymicrobial infection	64 (44.4)	48 (45.7)	16 (43.2)	0.795	0.905 (0.465-1.926)	0.795	54 (44.3)	9 (47.4)	0.829	1.113 (0.423-2.930)	0.829
SURGICAL MANAGEMENT											
Initial surgical strategy	140 (97.2)	103 (98.1)	36 (97.3)	1.000	0.699 (0.062-7.942)	0.773	120(98.4)	18 (94.7)	0.352	0.298 (0.026-3.451)	0.332
Conservative treatment	31/140 (22.1)	20/103 (19.4)	11/36 (30.6)	0.167	1.826 (0.772-4.319)	0.170	25/120 (20.8	6/18 (33.3)	0.228	1.920 (0.656-5.621)	0.234
1-stage cranioplasty	8/140 (5.7)	8/103 (7.8)	0 (0)	0.112	NC	nC	7/120 (5.8)	0 (0)	0.596	NC	
Bone flap removal	102 /140 (72.9)	76/103 (73.8)	25/36 (69.4)	0.615	0.807 (0.351-1.859)	0.615	89/120 (74.2)	12 /18(66.7)	0.541	0.719 (0.249-2.076)	0.542
Duraplasty removal	18/103 (17.5)	14/75 (18.7)	4/27 (14.8)	0.774	0.758 (0.226-2.542)	0.653	15/87 (17.2)	3/14 (21.4)	0.709	1.327 (0.330-5.341)	0.690
Curettage of bone edges	104/131 (79.4)	78/95 (82.1)	25/35 (71.4)	0.183	0.545 (0.221-1.342)	0.197	91/111 (82.0)	11/18 (61.1)	0.041	0.342 (0.118-0.990)	0.048
ANTIMICROBIAL THERAPY											
Total duration (weeks)	12.7 (8.0-14.0)	13.0 (10.0-14.4)	11.9 (6.3-13.3)	**0.014**	0.991 (0.943-1.040)	0.709	12.9 (8.1-14.1)	12.6 (6.6-13.9)	0.398	1.011 (0.957-1.068)	0.703
Intravenous treatment	138 (95.8)	101 (96.2)	35 (94.6)	0.651	0.693 (0.122-3.950)	0.680	117 (95.9)	18 (94.7)	0.585	0.763 (0.084-6.908)	0.810
Duration of intravenous treatment (weeks)	5.1 (2.3-7.8)	4.9 (2.1-8.0)	5.1 (2.7-6.9)	0.993	0.988 (0.954-1.023)	0.503	5.0 (2.2-7.7)	4.7 (2.1-6.6)	0.664	0.993 (0.953-1.034)	0.719
Combination therapy	121 (84.0)	89 (84.8)	30 (81.1)	0.601	0.770 (0.289-2.053)	0.602	102 (83.6)	16 (84.2)	1.000	1.036 (0.276-3.888)	0.959

CI, confidence interval; OR, odd ratios.
Variables are expressed as percentages for dichotomous variables and as medians with interquartile range for continuous variables. In percentage calculation, the number of missing values was excluded from the denominator.
[a] Nonparametric tests were used to compare groups (chi-square, Fisher exact and Mann-Whitney U tests), as appropriate.
[b] Results of univariate regression analysis expressed as OR with their 95% CI.

93.1%). The main implicated pathogens were *S. aureus* (n = 64, 44.4%; including 2 [3.1%] methicillin-resistant isolates), *C. acnes* (n = 57, 39.6%), GNB (n = 40, 27.8%), and non-*aureus* staphylococci (n = 34, 23.6%; including 10 [29.4%] methicillin-resistant isolates).

Management of bone flap infection

All patients but four (97.2%) underwent surgery in a median delay of 17.1 (IQR, 5.7-39.3) weeks after presumed inoculation. Therefore, 121 (84.0%) cases were classified as chronic infections (evolution >4 weeks). Main surgical strategies consisted of bone flap removal (n = 102, 72.9%) or debridement with bone flap retention (n = 31, 22.1%). Curettage of bone edges was performed in 104/131 (79.4%) patients, and duraplasty was removed in 18/103 (17.5%) cases. When comparing the subsets of patients with bone flap removal and retention, conservative procedures were performed in less often chronic infections (n = 20 [64.5%] vs 91 [89.2%]; $P = 0.004$), with more frequent fever (n = 12 [38.7%] vs 20 [19.6%]; $P = 0.032$), and less sinus tract (n = 4 [12.9%] vs 45 [44.1%]; $P = 0.002$) and bone lysis (n = 2 [7.1%] vs 25 [25.5%]; $P = 0.038$).

Median duration of antimicrobial therapy was 12.7 (IQR, 8.0-14.0) weeks, with initial intravenous administration (n = 138, 95.8%) for 5.1 (IQR, 2.3-7.8) weeks. Combination therapy was used in 121 (84.0%) patients.

Outcome and determinants of treatment failure

During a median follow-up of 117.1 (IQR, 62.5-235.5) weeks, treatment failure occurred in 37/142 (26.1%) cases, including 16 (26.1%) infection persistence, three (8.1%) relapses and/or 22 (59.5%) superinfections. Twenty-four (64.9%) patients needed an additional surgical procedure. Thirteen (9.1%) patients died during follow-up, including two infection-related deaths. Eleven (8.9%) patients received suppressive antimicrobial therapy due to an estimated high risk of relapse.

Comparison of patients with or without treatment failure is presented in Table 1. In univariate analysis, determinants of treatment failure were the presence of a neurological deficiency (OR, 3.850 [95% CI, 1.202-12.336]; $P = 0.023$) and brain abscess (OR, 2.588 [95% CI, 1.168-5.738]; $P = 0.019$) (Figure 1, panels a and b). Antimicrobial therapy was significantly longer in successful procedures (12.7 vs 13.0 weeks, $P = 0.014$), but the length of treatment was not associated with outcome in regression analysis (OR, 0.991 [95% CI, 0.943-1.040]; $P = 0.709$).

Excluding superinfections, considered as different events than initial infection, 19 (13.4%) "specific" treatment failures were observed. Craniectomy for tumor removal (OR, 4.038 [95% CI, 1.119-14.578]; $P = 0.033$) and curettage of bone edges (OR, 0.342 [95% CI, 0.118-0.990]; $P = 0.048$) were significantly associated with outcome (Figure 1, panels c and d).

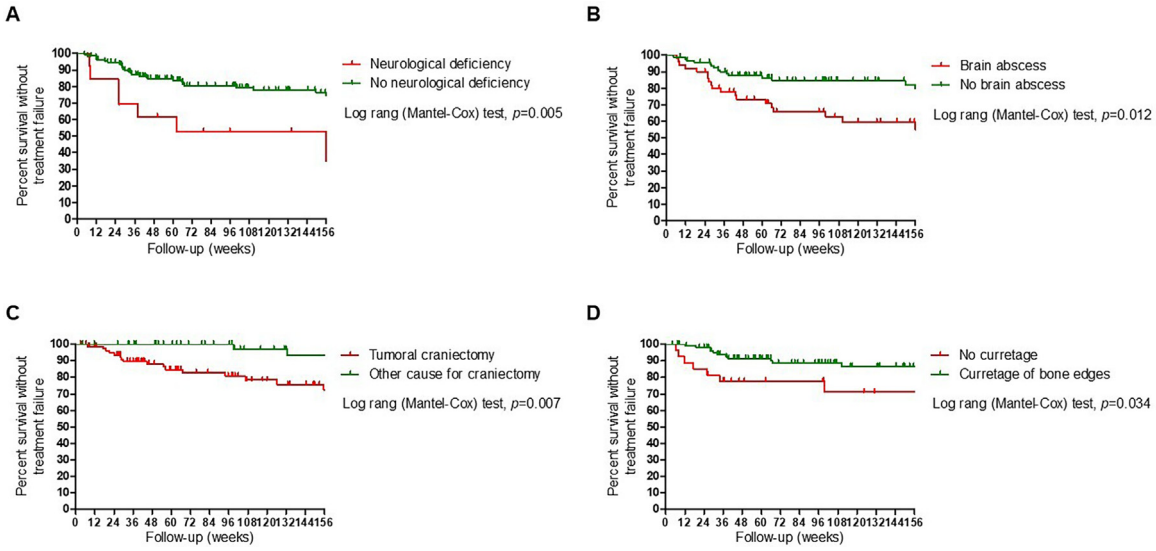

Figure 1. Kaplan-Meier survival curves for probability of survival without treatment failure, according to the main determinants of outcome.

Regarding specifically the 31 patients treated with debridement and bone flap retention, 11 (35.5%) failures were observed, including six (19.4%) "specific" failures when excluding superinfections, with no significant difference compared to bone flap removal (25 [24.8%] failures [$P = 0.253$], 12 [11.9%] when excluding superinfections [$P = 0.299$]). However, this subset of patients required more additional surgical procedures for septic reasons (n = 9 [29.0%] vs 14 [13.4%]; $P = 0.055$) and long-term suppressive antimicrobial therapy (n = 6 [22.2%] vs 5 [5.4%]; $P = 0.008$). Presence of cerebral abscess (OR, 10.625 [95% CI, 1.484-76.081], $P = 0.019$) was the only determinant of failure in conservative procedures. Of note, rifampin-based therapy (n = 11, 35.5%), and especially rifampin-fluoroquinolone combination (n = 9, 29.0%), was not associated with outcome in staphylococci infections treated with bone flap retention. Two (33.3%) of the six patients receiving long-term suppressive antimicrobial therapy after bone flap retention experienced treatment failure.

In patients with bone flap removal, secondary reconstruction was performed in 61 (59.8%) cases, with a median delay of 41.3 (IQR, 30.0-60.0) weeks after flap removal, and 28.0 (IQR, 20.0-46.3) weeks after the end of antimicrobial therapy. Reconstructions were mostly performed using custom-made hydroxyapatite cranioplasty (n = 36, 62.1%), which was associated with a lower failure rate (OR, 0.195 [95% CI, 0.044-0.859]; $P = 0.031$) than other biomaterials (bone cement [n = 8, 13.8%], titanium [n = 6, 10.3%]) or autologous cranioplasty (n = 6, 10.3%).

Discussion

To our knowledge, this is the largest study describing the management of bone flap-related osteomyelitis after cranioplasty. Despite limitations inherent to its retrospective and monocentric design, including heterogeneity of the included patients and their management, our series provides important insights into bone flap-related osteomyelitis after cranioplasty.

Diagnosis

The diagnosis of bone flap-related osteomyelitis should be suspected in the presence of any wound event, sinus tract, or other wound disorders being the most prevalent clinical symptoms. As previously described, the absence of fever or biological inflammatory syndrome should not lead to ruling out the diagnostic [14–16]. CT scan or magnetic resonance imaging should be performed to preclude empyema or brain abscess, present in almost half of the patients in our series. Additional radiological signs of bone infection such as bone lysis can be present. However, as shown in a recent meta-analysis, bone lysis is not specific for bone flap osteomyelitis as up to 25% of patients can present aseptic bone resorption after cranioplasty, especially in young individuals, after severe brain trauma and for fragmented flaps [17]. Based on the experience of other bone and joint infections, microbiologic diagnosis should rely on multiple deep surgical samples. Pathogens implicated in cranioplasty infection have poorly been described. As expected, we highlighted a predominance of staphylococci, as in previously published smaller cohorts [7,18–20]. The present description of a larger number of patients, especially focusing on bone infection, allows us to more precisely describe the bacteriological etiology of these infections, with some important findings: (i) *Cutibacterium acnes* represents a major causative agent as in other upper-body bone and joint infections [20,21], as known to frequently colonize bone flaps in delayed autologous cranioplasties even if not predictive for subsequent infection [22]; (ii) as for prosthetic joint infection, non-*aureus* staphylococci are highly prevalent, and associated with a high level of methicillin resistance; and (iii) GNB were found in more than a quarter of cases. Consequently, methicillin-resistant staphylococci and GNB should be systematically included in the spectrum of the empirical antimicrobial therapy initiated after surgery.

Clinical management

The management of bone flap-related osteomyelitis after cranioplasty is challenging, with a global failure rate of 35.5% despite complex medico-surgical management. This high rate of unfavorable outcomes must be interpreted in light of the strict definition used for failure—including persistence, relapse, and superinfection—and the prolonged follow-up exceeding 2 years. Additionally, in the absence of guidelines, indications of flap and dura mater plasty removal were left at the appreciation of the treating surgeon, which could constitute a bias in the choice of surgical strategies. Following this study, a dedicated multidisciplinary meeting to discuss surgical and medical strategies has been implemented and is under evaluation. In another retrospective cohort study focusing more on one- and two-stage surgical procedures and including only 35 patients, Gold et al. described a failure rate

of 11.4%, with no persistence tracking with systematic culture at time of cranioplasty [23].

Cornerstone of the management of complex bone and joint infection relies on surgical reduction of bacterial inoculum. Based on periprosthetic joint infection guidelines [12], the most common strategy consists of extensive debridement and bone flap removal before delayed reconstruction, especially for chronic infections [10]. Pathophysiological rationale of this assertion is based on the complex interaction between immune system and biofilm-embedded bacteria on implant or necrotic bone, leading to reduced bacterial clearance and limiting antimicrobial efficacy [24]. Nevertheless, these two-stage strategies are associated with complications—including sinking flap syndrome and direct brain trauma—and conservative treatment did not appear as a risk factor for failure, and has already been proposed with success [23,25]. Bone flap retention was however associated with a higher need for additional surgery and long-term suppressive antimicrobial therapy. The safe conditions for such conservative treatment remain to be determined, but a complete debridement of the infected tissues must be proposed [25], including curettage of bone edges, which appeared as a protective factor in our series. Another issue surrounding surgical debridement is the management of the plasty of dura mater, with a risk of neurological lesions associated with its removal in the context of important local inflammation. Our findings showed no association between duraplasty removal and outcome, while no other study has evaluated this specific question in the literature. Finally, for two-stage procedures, the ideal timing for reconstruction is also unknown. As shown by our results, we propose long intervals between antimicrobial treatment and new cranioplasty (≥3 months). Even if shorter intervals have been suggested, a recent retrospective cohort demonstrated a 10% decrease in reinfection per month of delay, making the interval of 3-6 months acceptable [26], consistent with other smaller series [27]. Regarding reconstruction, our results showed that hydroxyapatite was associated with a lower risk of failure. This finding is consistent with previous studies suggesting that this bone substitute might prevent bacterial adhesion and biofilm formation, and consequently reduce the (re)-infection risk [28–32].

Regarding medical management, patients included in our cohort received a 3-month course of antimicrobial therapy, reflecting the current expert proposals for neurosurgical implant-associated infections and guidelines for periprosthetic joint infection [10,12]. Shortening treatment duration to 6 weeks might be conceivable in case of complete removal of foreign material, as proposed in vertebral osteomyelitis [33]. However, there is currently no data allowing choosing optimal treatment duration. Shortening antimicrobial duration has not been possible in other device-associated infections such as prosthetic joint infection [34]. The nature of antimicrobial therapy did not affect outcomes in our series, including intravenous route or combination therapies. Interestingly, in a cohort of 103 infections after cranial neurosurgery, including 15 bone flap-associated and 12 device-associated infections, the only significant prognostic factor was the use of “adequate” antimicrobial therapy, i.e., comprising a molecule active against biofilm-embedded bacteria: rifampin for staphylococci and fluoroquinolone for GNB [16]. In our series, the use of rifampin-based combination therapy, especially with fluoroquinolones, was not associated with a better outcome in staphylococci infections, including those treated with flap retention.

In summary, bone flap-related osteomyelitis after cranioplasty requires complex and poorly codified medico-surgical management, associated with a high risk of failure. Surgical debridement—including curettage of bone edges—is essential, with a possible role for conservative treatment under conditions that remain to be defined. The spectrum of postoperative empirical antimicrobial therapy should include staphylococci—including methicillin-resistant non-*aureus* staphylococci isolates—*Cutibacterium acnes* and GNB. Optimal nature and duration of targeted antimicrobial therapy are unknown. All these uncertainties advocate for multidisciplinary management, to coordinate radiologists, microbiologists, infectious disease physicians, and neurologic surgeons toward the most appropriate individualized strategy.

Declaration of competing interest

The authors have no competing interests to declare.

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Ethical approval

This study (ClinicalTrials.gov registration number NCT05367713) received the approval of the Scientific and Ethical Committee of Hospices Civils de Lyon (reference n°22_5682). All patients received written information about the study. No written informed consent was required for inclusion.

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Author contributions

All authors participated in patients’ management and inclusion, and in writing and editing the manuscript, and have read and approved the final version of the manuscript. VD collected data. VD and FV performed the statistical analysis. FV conceived and supervised the study.

Transparency declaration

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